Cognitive-neurophysiological markers of ADHD
Developmental pathways and comparison with bipolar disorder

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Cognitive-neurophysiological markers of ADHD: developmental pathways and comparison with bipolar disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder associated with wide-ranging impairments in cognitive and brain functions. This thesis uses a multi-disciplinary approach to study cognitive and neurophysiological impairments in ADHD in adolescence and adulthood. The first part of this thesis examines the developmental and aetiological pathways of cognitive and electrophysiological (EEG) measures in a follow-up sample of adolescents and young adults with a childhood diagnosis of ADHD, their siblings and age-matched controls. The findings suggest that cognitive and event-related potential (ERP) indices of attention-vigilance and error processing are markers of ADHD remission, distinguishing between individuals with persistent and remitted ADHD at follow-up. Instead, cognitive and ERP measures mapping onto executive and conflict-monitoring processes, and indices of brain functional connectivity during cognitive performance are insensitive to ADHD outcome, as they do not differentiate the remitted and persistent ADHD groups. By examining the aetiological structure of a broad range of cognitive and ERP measures sensitive to differences between individuals with persistent ADHD and controls, this thesis further shows that impairments in these measures map onto three partially separable aetiological processes, which show moderate-to-large overlap with the aetiological influences on ADHD. The second part of this thesis examines how cognitive-neurophysiological profiles differ between women with ADHD, women with bipolar disorder (BD) and control women, to identify impairments that are specific to or shared between ADHD and BD. The findings provide evidence for multiple commonalities in cognitive and EEG measures of attentional processes and inhibitory control. A few impairments distinguishing between the disorders also emerged, which, if replicated, may represent candidate biomarkers to help dissociate ADHD from BD. Overall, by using a combination of cognitive, neurophysiological, developmental and sibling-modelling approaches, this thesis furthers our understanding of the developmental and aetiological pathways to ADHD, and of the specificity of atypical cognitive and neural profiles in adolescents and adults with the disorder.

Statement of authorship

The present thesis represents my own work, from two collaborative projects based at the Social, Genetic and Developmental Psychiatry (SGDP) Centre. The results in Chapters 2, 3 and 4 include data from a follow-up project of an ADHD and control sibling-pair sample (Sibling EEG Follow-up Study [SEFOS]; PI: Professor Jonna Kuntsi). The SEFOS project was supported by generous grants from Action Medical Research and the Peter Sowerby Charitable Foundation (grant reference GN1777). The research presented in Chapter 3 was further supported by a Short-term fellowship from the European Molecular Biology Organization (EMBO), awarded to myself to undertake a two-month research visit to the University of California, Los Angeles (UCLA). The results included in Chapters 5 and 6 are based on data from a cross-disorder comparison study between ADHD and BD (Female Experiences and Brain Activity [FEBA]; PI: Professor Jonna Kuntsi), primarily supported by an Economics and Social Research Council (ESRC) studentship awarded to Dr Viryanaga (formerly Glenn) Kitsune (grant reference ES/100971X/1).

Data collection for SEFOS and FEBA was completed by the respective research teams before I started my PhD. For Chapter 2, I formulated the research questions, processed data, conducted analyses and interpreted the findings under the guidance of supervisor Professor Jonna Kuntsi and Dr Viryanaga Kitsune, with further advice from Dr Celeste Cheung, Dr Gráinne McLoughlin and Professor Philip Asherson. For Chapter 3, I secured additional funding, formulated new research questions for secondary analyses, processed data, programmed and ran new EEG connectivity analyses, and interpreted the results under the guidance of Dr Iman Mohammad-Rezazadeh (UCLA) and supervisor Professor Jonna Kuntsi, with further advice from Dr Ioannis Bakolis, Joseph Jurgiel (UCLA) and Professor Sandra Loo (UCLA). For Chapter 4, I formulated the research questions, planned and ran the preliminary and multivariate model-fitting analyses, and interpreted the findings under the guidance of supervisor Professor Jonna Kuntsi, Dr Frühling Rijsdijk and Dr Celeste Cheung, with further advice from Professor Philip Asherson. For Chapters 5 and 6, I formulated the research questions, processed data, programmed and conducted new EEG time-frequency analyses and interpreted the results under the guidance of Professor Jonna Kuntsi, with advice from Dr Viryanaga Kitsune, Professor Philip Asherson, Dr Gráinne McLoughlin (Chapter 5) and Professor Daniel Brandeis (Chapter 6).

Publications relevant to this thesis

Sections of *Chapter 1* are adapted from a section I wrote for the following publication in submission:

Franke B, **Michelini G**, Asherson P, Banaschewski T, Bilbow A, Buitelaar JK, Cormand B, Faraone SV, Ginsberg Y, Haavik J, Kuntsi J, Larsson H, Lesch KP, Ramos-Quiroga JA, Rethelyi JM, Ribases M, Reif A (in submission). Developmental trajectories of ADHD across the lifespan – a comprehensive review. *European Neuropsychopharmacology.*

Chapter 2 is based on the following publication (available under the Creative Commons licence):

Michelini G*, Kitsune GL*, Cheung CHM, Brandeis D, Banaschewski T, Asherson P, McLoughlin G, Kuntsi J (2016). Attention-deficit/hyperactivity disorder remission is linked to better neurophysiological error detection and attention-vigilance processes. *Biological Psychiatry*, 80, 12, pp. 923-932.

Chapter 3 is adapted from the following publication:

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Chapter 4 is adapted from the following publication:

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Chapter 5 is based on the following publication (available under the Creative Commons licence):

Michelini G, Kitsune GL, Hosang GM, Asherson P, McLoughlin G, Kuntsi J (2016). Disorder-specific and shared neurophysiological impairments of attention and inhibition in women with ADHD and women with bipolar disorder. *Psychological Medicine*, 46, 3, pp. 493-504.

Chapter 6 is adapted from the following publication:

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CHAPTER 1 - Introduction

1.1 Abstract

In this introductory chapter, I will provide an overview of attention-deficit/hyperactivity disorder (ADHD), in relation to its diagnostic criteria, epidemiology, developmental presentations, co-occurring symptoms and disorders, and aetiology. I will then review the methods used to investigate cognitive and neurophysiological impairments in ADHD, as well as the available literature on these impairments in children and adults with the disorder. This overview will then focus on bipolar disorder (BD), its similarities with ADHD, and review previous research investigating cognitive-neurophysiological biomarkers that could help identify overlapping and distinct characteristics of the two disorders. Finally, I will conclude with a summary of the specific aims of this thesis, and provide an overview of how the following chapters will address my research questions.

1.2 Introduction to ADHD

ADHD is a neurodevelopmental disorder characterised by developmentally inappropriate levels of inattentive and/or hyperactive-impulsive symptoms, which significantly interfere with individuals' lives. The first reference in the medical literature to the syndrome that today is known as ADHD was recorded by the German physician Melchior Adam Weikard, in a book chapter published in 1775 describing children with attention disorders (Barkley and Peters, 2012). Following the first documentations of case studies on children displaying inattentive and hyperactive-impulsive behaviours, the twentieth century has seen a rise of efforts to describe psychiatric conditions based on empirical evidence. The American Psychiatric Association (APA) included ADHD (referred to as "hyperactive child syndrome") in the Diagnostic and Statistical Manual (DSM) of Mental Disorder for the first time in its second edition (DSM-II) (APA, 1968). This early description was updated in the third edition, DSM-III (APA, 1980), which replaced the aetiological formulations of mental health disorders (strongly influenced by psychoanalytic theories) with atheoretical descriptions of symptoms (Shorter, 2015). This version of the DSM placed equal emphasis on both inattentive and hyperactive-impulsive symptom dimensions of ADHD, and acknowledged the heterogeneity of symptom presentations that characterises the

disorder (APA, 1980). This recognition of the complexity and variability in presentation subsequently led to the first distinction between ADHD subtypes (inattentive, hyperactive-impulsive and combined subtypes) in the DSM-IV and its revised version, DSM-IV-TR (APA, 1994, APA, 2000). Finally, the latest version of the DSM, DSM-5, has included further description of ADHD also in adulthood, and more explicitly acknowledged the possible comorbidity with commonly co-occurring disorders, such as autism spectrum disorder (ASD) (APA, 2013). This edition has also raised the age of onset of symptoms from 7 years to 12 years, to acknowledge the possible emergence of ADHD symptoms in pre-adolescence, and lowered the minimum number of symptoms needed for diagnosis in adults, from six to five symptoms of either inattention or hyperactivity-impulsivity. Finally, the three ADHD subtypes have been termed "presentations" in the DSM-5, in light of research showing that subtypes of ADHD diagnosis may not be as stable over time as previously thought (Willcutt et al., 2012).

1.2.1 Diagnosis and symptoms of ADHD

The diagnostic criteria for ADHD employed in this thesis are based on the DSM-IV-TR (APA, 2000), which was the current DSM version at the time that the studies included in this thesis were planned and set up. The DSM-IV-TR includes 18 symptoms of ADHD: nine symptoms of inattention, six symptoms of hyperactivity and three symptoms of impulsivity (Table 1.1). The nine inattentive symptoms and the combination of the six hyperactive and three impulsive symptoms are grouped into inattentive and hyperactive-impulsive subscales, respectively. According to the DSM-IV-TR, a diagnosis of ADHD is met if an individual shows at least six symptoms of inattention and/or hyperactivity-impulsivity for at least 6 months, and if these symptoms are manifested before the age of 7 years. Additionally, these symptoms need to be associated with significant functional impairment across at least two settings (e.g., at home and at school), not to occur exclusively during the course of a pervasive developmental or psychotic disorder, or be better explained by another psychiatric condition. Three subtypes of ADHD diagnosis can also be made: predominately inattentive type (ADHD-IA), if at least six inattentive symptoms (but less than six hyperactive-impulsive symptoms) are present; predominately hyperactive-impulsive type (ADHD-HI), if at least six hyperactive-impulsive symptoms (but less than six inattentive symptoms) are present; and ADHD combined type (ADHD-C), if at least six symptoms are present on both symptom domains. An adult may be diagnosed according to DSM-IV-TR if they met diagnostic criteria in childhood, if symptoms were manifested before the age of 7 and if symptoms are met in full during adulthood.

Similar diagnostic criteria are included in the International Classification of Diseases (ICD-10), an alternative diagnostic system (not used in this thesis) by the World Health Organization (WHO) (WHO, 1992). In the ICD-10, ADHD is referred to as "hyperkinetic disorder" and defined by the presence of symptoms from all three symptom dimensions of inattention, hyperactivity and impulsivity. This diagnostic classification therefore identifies a more severe form of ADHD, and is considered more stringent than the DSM (Sorensen et al., 2005).

Table 1.1. DSM-IV-TR diagnostic criteria for ADHD

(A1) Inattention: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
1 Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities
2 Often has difficulty sustaining attention in tasks or play activities
3 Often does not seem to listen when spoken to directly
4 Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure of comprehension)
5 Often has difficulty organising tasks and activities
6 Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
7 Often loses things necessary for tasks or activities at school or at home
8 Is often easily distracted by extraneous stimuli (may include unrelated thoughts)
9 Is often forgetful in daily activities
(A2) Hyperactivity-impulsivity: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Hyperactivity:
10 Often fidgets with hands or feet or squirms in seat
11 Often leaves seat in classroom or in other situations in which remaining seated is expected
12 Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to feeling restless)
13 Often has difficulty playing or engaging in leisure activities quietly
14 Often talks excessively
15 Is often "on the go" or often acts as if "driven by a motor"

Impulsivity:
16 Often has difficulty awaiting turn in games or group situations
17 Often blurts out answers to questions before they have been completed
18 Often interrupts or intrudes on others, e.g., butts into other children's games
Other criteria for diagnosis:
a) Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
b) Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
c) There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
d) The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder).

Note: Items replicated from the revised version of the DSM-IV (DSM-IV-TR; APA, 2000).

1.2.1.1 Categorical and dimensional approaches

The DSM criteria use a categorical classification of mental illnesses, including ADHD, with a binary definition of disorders (i.e., present/absent). This binary definition reflects the binary nature of treatment decisions in clinical practice, allows clear diagnostic decisions and has the advantage of allowing clear and effective communication between professionals in health care and research settings (Coghill and Sonuga-Barke, 2012, Barkley, 1998). Despite its practical advantages, this categorical approach is deemed not to take into account the notion that most psychiatric disorders may represent the impaired end of a distribution of traits that vary continuously throughout the general population, rather than qualitatively different entities (Larsson et al., 2012, Plomin et al., 2009). An alternative definition of ADHD, based on dimensional approaches to mental illnesses, builds on this notion, and posits that inattentive and hyperactive-impulsive behaviours reflect continuous traits rather than a categorical disorder, which may reach clinical levels only in individuals with the most severe and impairing presentations (Shah and Morton, 2013, Asherson et al., 2016, Faraone and Biederman, 2016). This dimensional approach may better reflect the continuous nature of ADHD psychopathology and associated cognitive and neurophysiological impairments, as well as of the involved neurobiological systems and the multifactorial aetiology that underlies the disorder (Shaw et al.,

2011, Anokhin et al., 2008, de Geus, 2010, Polderman et al., 2006). The dimensional approach is supported by research studies showing that the aetiological contribution of genetic factors to ADHD (Chen et al., 2008, Larsson et al., 2012), as well as to the association between the disorder and cognitive impairments (Kuntsi et al., 2010, Kuntsi et al., 2014), is the same for the categorical/binary and dimensional/continuous definitions of ADHD symptoms. Recent initiatives, such as the Research Domain Criteria (RDoC) framework by the National Institute of Mental Health (NIMH) in the USA, have promoted a paradigm shift to develop a new classification of mental diseases based on a dimensional approach (Insel et al., 2010). Such a system, however, may be difficult to implement in clinical practice, as it may provide a less straightforward distinction between affected and unaffected individuals, and thus limited utility for diagnostic and treatment decisions (Brown and Barlow, 2005). Nonetheless, both categorical and dimensional approaches to ADHD present advantages and disadvantages, and may provide two valuable perspectives to describing and studying ADHD and its underlying pathophysiology. Both approaches are employed to study ADHD in this thesis.

1.2.1.2 Parent-, teacher- and self-reports

Depending on the age of an individual, different informants may provide reports of ADHD symptoms and functional impairments in clinical and research settings. In childhood and adolescence, clinical guidelines recommend collecting reports from parents and teachers (Taylor et al., 2004). Research shows that the agreement between reports of ADHD symptoms from different informants is typically only moderate (correlation estimates ranging between 0.30 and 0.50) (Goodman, 2001, Achenbach and Rescorla, 2001). This low agreement likely reflects partially different information and point of views provided by each informant, who might report on child's behaviour in different settings (e.g., parents at home, teachers at school). Since one of the requirements for diagnosis is that the symptoms are observed in at least two contexts (APA, 2013, WHO, 1992), accounts from multiple informants are valuable and should be integrated with the interviewer's perspective both in clinical and research settings, to obtain a complete evaluation of behaviour of the individual concerned (Taylor et al., 2004).

In adulthood, the difficulty of collecting multi-informant reports means that diagnoses often solely rely on self-report (Asherson, 2005). Although self-reports are recommended as the primary source of information for adult diagnosis in clinical settings (Kooij et al., 2010), empirical data show that young adults with ADHD may underestimate or lack insight into their problems, leading to concerns about the accuracy of their accounts (Knouse et al., 2005, Faraone and Biederman, 2016). The potentially lower reliability of self-ratings is considered the reason why

twin studies show higher heritability for parent- compared to self-rated ADHD symptoms (Chang et al., 2013, Larsson et al., 2013, Merwood et al., 2013): since low reliability leads to increased measurement error, which in the twin method is captured by factors that are not shared between twins, this in turn imposes a ceiling on heritability estimates (Merwood et al., 2013, Faraone and Biederman, 2016). In addition, while the DSM-5 has included more age-appropriate descriptions and examples of ADHD symptoms in adulthood (Asherson et al., 2016, APA, 2013), these still rely on behavioural descriptions of symptoms, which can be affected by rater effects. Considering the potential rater biases of subjective clinical accounts, research efforts have been conducted to assess the utility of objective measures (Groom et al., 2016, Hall et al., 2016, Lenartowicz and Loo, 2014), such as indices of cognitive and brain function, as possible aids in the diagnostic process (as discussed later in this chapter in section 1.3).

1.2.2 Epidemiology

1.2.2.1 Prevalence

Meta-analytic evidence shows that ADHD affects 5-7% of children and adolescents, and 2-4% of adults worldwide (Polanczyk et al., 2007, Simon et al., 2009, Willcutt, 2012). Further evidence indicates that, over the last three decades, the prevalence of ADHD diagnoses in childhood has remained unchanged (Polanczyk et al., 2014, Collishaw, 2015), despite increases in prescriptions of medication for ADHD over time (Dalsgaard et al., 2015). While the disorder was originally believed to be a largely childhood-limited condition (Hill and Schoener, 1996), increasing recognition has been given to adult ADHD (Asherson et al., 2016, Faraone et al., 2006), as also reflected in the DSM-5 (APA, 2013).

One main reason for the lower prevalence of ADHD in adulthood compared to childhood is that ADHD may remit with development (as discussed in detail in the next section). Another possible explanation is low recognition of ADHD in adulthood, leading to an under-diagnosis. Until the DSM-5, the symptoms of ADHD included in the DSM were based on behavioural descriptions developed for ADHD in children (APA, 2000, APA, 2013). However, symptoms of hyperactivity-impulsivity in adulthood are often manifested with feelings of restlessness or inner tension (Asherson et al., 2014, Kooij et al., 2010, Haavik et al., 2010), which may not be fully captured by DSM symptoms, especially prior to the DSM-5. In addition, the relatively low recognition and experience of clinicians specialised in adult psychiatry with ADHD symptoms may result in adults with ADHD being misdiagnosed and assigned more typical adult psychiatric conditions (Asherson et al., 2014, Asherson, 2005).

1.2.2.2 Developmental presentations and trajectories of ADHD

As mentioned above, the lower prevalence of ADHD in adulthood than in childhood or adolescence may reflect diagnostic remission with development. ADHD symptoms, especially hyperactivity-impulsivity (van Lieshout et al., 2016b, Pingault et al., 2015), tend to naturally decline with age (Faraone et al., 2006). Longitudinal studies have shown that ADHD may remit in adolescence or adulthood, although studies are inconsistent with regard to the persistence/remission rate of the disorder. A meta-analysis of longitudinal studies have shown that ADHD may persist in young adulthood in 15% of cases, with a further 50% of cases meeting criteria for partial remission (Faraone et al., 2006). More recent follow-up studies of children diagnosed with ADHD-C, however, have reported higher persistence rates (around 80%) into adolescence and young adulthood (Cheung et al., 2015, van Lieshout et al., 2016b). The persistence rates are significantly lower in recent population-based studies (1.5-10%) (Agnew-Blais et al., 2016, Moffitt et al., 2015, Caye et al., 2016a, Riglin et al., 2016).

One possible reason for the discrepancies between longitudinal studies on the persistence of ADHD may be found in the way remission and persistence are defined (Caye et al., 2016b). As described above (section 1.2.1.2), there is typically a change in the source of information used for ADHD diagnoses across development (parent- and teacher-reports in childhood and adolescence, self-reports alone in adulthood). A recent study has shown that ADHD persistence rates in early adulthood varied from 1.9% to 61.4% when using different combinations of information source (parent- vs self-report), method (rating scale vs interview) and symptom threshold (DSM vs norm-based) (Sibley et al., 2016). Follow-up studies of clinical samples in young adulthood based on self-report generally find lower rates of persistence of ADHD than studies using informant-report alone or in combination with self-report (Barkley et al., 2002, Wolraich et al., 2005, Biederman et al., 2009, Biederman et al., 2012, Du Rietz et al., 2016, van Lieshout et al., 2016b, Klein et al., 2012). On the one hand, the lower persistence and prevalence of adult ADHD based on self-report may represent an under-diagnosis due to false negatives (Ginsberg et al., 2014), given that individuals with ADHD may lack insight into their problems (Knouse et al., 2005, Faraone and Biederman, 2016). On the other hand, the higher persistence rate in clinical samples using informant-reports may result from informants (usually parents) over-estimating ADHD persistence due to not being aware of a decline in ADHD symptoms and impairments in their son/daughter after they leave the family environment. The use of self-reports may explain the low persistence rates in the recent population-based studies (Agnew-Blais et al., 2016, Moffitt et al., 2015, Caye et al., 2016a, Riglin et al., 2016). These studies are also based on non-clinically referred individuals for whom treatment was not sought for their

ADHD symptoms and impairment in childhood. As such, these population samples may not be fully representative of typical ADHD patient populations, but rather capture milder or transient forms of ADHD, which may be more likely to remit with development. Some of these studies have also ascertained ADHD in childhood and its persistence at follow-up only with reports on ADHD symptoms, rather than based on ADHD diagnosis (meeting criteria for both ADHD symptoms and impairment) (Riglin et al., 2016, Caye et al., 2016a), which may result in biased estimates.

New evidence from recent population-based studies has raised the possibility that adults with ADHD may not always meet ADHD diagnoses in childhood (Agnew-Blais et al., 2016, Moffitt et al., 2015, Caye et al., 2016a), as required before the age of 12 years according to current DSM criteria (APA, 2013). These studies have proposed that ADHD may not always be the continuation of childhood ADHD, but instead emerge in late adolescence or adulthood, and potentially represent a distinct diagnostic entity from childhood ADHD (Agnew-Blais et al., 2016, Moffitt et al., 2015, Caye et al., 2016a). This is currently a topic of some controversy, with other authors suggesting that these studies may have overestimated the prevalence of adult-onset ADHD cases (Asherson et al., 2016, Faraone and Biederman, 2016). While childhood diagnoses were based on reports from parents and teachers, adult ADHD diagnoses relied on self-reports, which may have resulted in less reliable accounts of symptoms and impairments, and thus, potentially, led to false positives. In addition, it has been proposed that some children may manifest sub-threshold ADHD symptoms instead of the full-blown disorder thanks to the presence of positive external scaffolding or protective factors (e.g., high IQ, supportive family environment) (Faraone and Biederman, 2016). Since ADHD can be considered an extreme form of a dimensional trait, accumulation of risk factors across development may lead individuals with this positive scaffolding to exceed the diagnostic cut-offs only at later developmental stages, such as when they leave their family environment and face the new challenges of their adult lives (Faraone and Biederman, 2016). Further investigation into the characteristics of adult cases who do not meet ADHD criteria in childhood is needed, in order to clarify the nature of adult-onset ADHD (Asherson et al., 2016).

1.2.2.3 Gender differences

A difference across development exists in the ratio of males and females affected by ADHD (Willcutt, 2012). The disorder is more prevalent in boys than in girls in childhood, with gender ratios ranging from 3:1 in population-based studies to 9:1 in clinical populations (Willcutt, 2012, Polanczyk et al., 2007, Gaub and Carlson, 1997, Staller and Faraone, 2006). In adults, however,

a more similar prevalence of ADHD has been reported in both genders, with gender distributions ranging from 1:1 to 1.6:1 (Faraone and Biederman, 2005, Kessler et al., 2006, Das et al., 2012).

One possible reason for the lower rate of affected females in childhood is that ADHD in girls may represent a less severe version of the disorder in boys (Gaub and Carlson, 1997, Arnett et al., 2015). However, evidence is inconsistent with regard to sex differences in symptom severity, with some studies reporting greater severity in boys with ADHD than in girls (Gaub and Carlson, 1997, Arnett et al., 2015), but others finding no differences (Novik et al., 2006) or greater severities in girls (Elkins et al., 2011). It has further been proposed that the lower prevalence of ADHD in girls than boys may be the result of an underrepresentation of girls with ADHD, produced by gender-based referral bias (Biederman, 2005). Current ADHD criteria may better reflect the typical behavioural manifestations of ADHD in boys than in girls (Skogli et al., 2013, Ohan and Johnston, 2005, Staller and Faraone, 2006). ADHD in girls is less commonly manifested with hyperactive-impulsive symptoms or accompanied by disruptive behaviours (Biederman et al., 2002, Willcutt et al., 2012, Thorell and Rydell, 2008), which often are the reasons leading to clinical referral in childhood. Since adult ADHD cases are often self-referred, in contrast to childhood ADHD which is often brought to the attention of clinicians by parents and teachers, a more similar number of women and men may self-refer to mental health services (Biederman et al., 1994, Biederman et al., 2004a), leading to a more equal balance in gender ratios in adulthood. Yet, women may be more likely to self-refer than men (Arcia and Conners, 1998, Biederman et al., 1994), which may result in a more equal prevalence across the genders in adults due to possible under-diagnosis in adult men.

An alternative explanation for the discrepancies in gender ratio in children but not in adults is the “female protective model” of neurodevelopmental disorders (Jacquemont et al., 2014), which proposes that, to be manifested in females, ADHD requires higher exposure to risk factors than in boys. This model is supported by recent empirical data from population-based twin samples, which found that co-twins of girls with ADHD had increased ADHD traits compared to co-twins of boys with ADHD (Taylor et al., 2016). These results suggest that girls with ADHD, compared to boys, may thus carry a greater burden of familial risk factors for ADHD, as indicated by greater ADHD symptoms in their co-twins. Due to the lower baseline levels of risk compared to boys, girls may require more time than boys to accumulate sufficient risk factors and manifest full-blown ADHD symptoms and impairment needed to exceed clinical cut-offs (Faraone and Biederman, 2016). As such, girls may have a later onset of ADHD than boys, as supported by one of the studies proposing the existence of late-onset ADHD (Agnew-Blais et al., 2016). A further

possible hypothesis is that more boys than girls may remit from childhood to adulthood, leading to a more similar gender distribution in adults. Most longitudinal studies, however, found similar persistence rates into early adulthood in males and females, thus not supporting this hypothesis (Agnew-Blais et al., 2016, Biederman et al., 2004a).

Overall, although discrepancies exist between gender ratios in childhood and adulthood, clear empirical evidence on the reasons for these inconsistencies is still limited. More generally, the higher prevalence of ADHD in boys than girls has led several large-scale studies on ADHD to largely focus on male populations (Chen et al., 2008, Kuntsi et al., 2010, Doyle et al., 2000, Klein et al., 2012). Empirical evidence is more limited on girls and women with ADHD to date, especially in terms of impairments in cognitive and brain functions.

1.2.2.4 Co-occurring symptoms and disorders

ADHD is often associated with symptoms of other disorders, which in some cases may lead to additional diagnoses (Asherson et al., 2016). It has been shown that over half of children with ADHD have at least one psychiatric comorbidity (Kraut et al., 2013, Larson et al., 2011, Jensen and Steinhausen, 2015). These high rates of comorbid symptoms and disorders have been observed both in population samples (Michelini et al., 2015, Pinto et al., 2016, Kadesjo and Gillberg, 2001, Jensen and Steinhausen, 2015) and in clinical samples (Skirrow and Asherson, 2013, Kitsune et al., 2016, Cooper et al., 2014).

In children, ADHD is often comorbid with conduct disorder and oppositional defiant disorder. These disorders may occur in around 10-70% of children and adolescents with ADHD (Biederman et al., 1991, Larson et al., 2011, Jensen and Steinhausen, 2015), and are more strongly associated with the hyperactive-impulsive symptoms of ADHD rather than the inattentive symptoms (Willcutt, 2012). A significant proportion of children with ADHD, around 15-65%, also show specific disorders of language, learning or motor development (Jensen and Steinhausen, 2015, Biederman, 2005, Fliers et al., 2009, DuPaul et al., 2013). In particular, dyslexia, dyscalculia and writing disorders are estimated to occur in 24% to 65% of children with ADHD (DuPaul et al., 2013). The comorbidity with ASD is also frequent, with studies showing that around 20-50% of those with ADHD also display ASD symptoms (Rommelse et al., 2011, Polderman et al., 2014). Anxiety disorders and internalising problems also co-occur in around 10-35% of ADHD cases, both in childhood and in adulthood (Biederman et al., 2013, Bowen et al., 2008), and may be more strongly related to the inattention symptom domain (Willcutt, 2012, Michelini et al., 2015). Comorbid symptoms of mood disorders and mood dysregulation are also common in individuals

with ADHD, especially in adulthood (Skirrow et al., 2012, Skirrow and Asherson, 2013). Depression and depressive symptoms co-occur in around 10-50% of adults with ADHD (Hesson and Fowler, 2015, Biederman et al., 2012, Goodman, 2009, Angold et al., 1999). Another common comorbid mood disorder in adulthood is bipolar disorder (BD), which has been shown to co-occur in 5% to 32% of adults with ADHD (Asherson et al., 2014, Halmoy et al., 2010). Moreover, ADHD and BD may present certain areas of symptomatic overlap, which in some cases may lead to difficulty in distinguishing ADHD from BD. The comparison between ADHD and BD is a major focus of this thesis (Chapters 5-6) and is discussed in detail in section 1.6.

1.2.3 Aetiology of ADHD

Similar to most quantitative traits and disorders (Plomin et al., 2009), ADHD is multifactorial disorder with a complex aetiological architecture, which arises from the interplay between genetic and environmental risk factors. Nearly three decades of quantitative genetic studies have established a large contribution of genetic factors on ADHD, but also a more limited role of individual-specific environmental influences (Burt, 2009, Burt et al., 2012). Building on this evidence, molecular genetic studies have set out to identify genetic variants associated with increased risk for ADHD (Faraone et al., 2005, Neale et al., 2010). Similarly, further research has tried to identify discrete environmental factors that may increase the risk of developing the disorder (Thapar and Rutter, 2009, Langley et al., 2005), and examined how these may interact with individuals' genetic predispositions.

1.2.3.1 Quantitative genetic studies

Quantitative genetic methods use the difference in genetic relatedness between family members to estimate the contribution of genetic and environmental factors to the variation of a trait or the covariation between two or more traits within a population (Rijsdijk and Sham, 2002). Specifically, quantitative genetic studies can quantify the role of additive genetic influences (A), non-additive (or dominant) genetic influences (D), environmental influences that make family members similar (shared environment, C; e.g., socio-economic status [SES]), and environmental influences that are individual-specific and make family members different (non-shared environment, E). The most commonly used quantitative genetic approach is the twin design, which is able to estimate the contribution of genetic and environmental factors by comparing monozygotic (MZ) and dizygotic (DZ) twins that are raised in the same family. MZ twins are genetically identical, while DZ twins share on average 50% of their segregating genes. Both sets of twins are assumed to be perfectly correlated for their exposure to shared

environmental factors of relevance for a trait under study (Mitchell et al., 2007, Rijsdijk and Sham, 2002). Due to the difference in genetic similarity between MZ and DZ pairs, twin studies can disentangle the contribution of A from C (or D, when non-additive genetic effects are present), as well as estimate the role of E, which is derived as the variance that makes MZ twins in the same pair different from one another (including measurement error). Sibling studies, which represent a type of family study, use siblings raised in the same family to decompose the variance of a trait into familial and non-familial influences. Since full siblings share on average 50% of their segregating genes and 100% of their shared environment, it is possible to decompose the variance/covariance of traits into contributions of familial influences (the combined effects of shared genetic and shared environmental effects) and non-familial influences (individual-specific effects and measurement error) (James et al., 2016, Kuntsi et al., 2010). Although sibling studies cannot distinguish between A and C influences, they are a powerful alternative to twin studies to study clinically-diagnosed disorders, where recruiting sufficiently large samples of affected twins may prove difficult. Further details of the sibling design can be found in Chapter 4, which uses this approach.

ADHD runs in families (Morrison and Stewart, 1971), as evident in the 2-to-8-fold increased risk for developing the disorder in first-degree relatives of individuals with ADHD (Biederman, 2005). Over the last three decades, many twin studies have explored the aetiological sources of individual differences in ADHD (Goodman and Stevenson, 1989, Kuntsi and Stevenson, 2001, McLoughlin et al., 2007, Nikolas and Burt, 2010). Heritability estimates across different studies of ADHD symptoms or diagnosis in childhood range between 0.60 and 0.90 (Burt, 2009, Nikolas and Burt, 2010, Faraone et al., 2005, Larsson et al., 2014), making ADHD one of the most highly heritable psychiatric disorders. Some studies suggested that dominance effects might also play a role (Rietveld et al., 2003, Wood et al., 2011). The familial co-segregation of ADHD traits may be largely due to genetic factors, as suggested by meta-analytic evidence indicating a negligible role of C influences (Burt, 2009, Nikolas and Burt, 2010). Environmental influences on ADHD are largely individual-specific and not shared between family members (Burt, 2009, Nikolas and Burt, 2010). Studies examining ADHD symptom domains separately have found similar heritability estimates for inattention and hyperactivity-impulsivity, and that the two dimensions are largely – but not perfectly – genetically correlated (r=0.55) (Greven et al., 2011, McLoughlin et al., 2007). Studies in late adolescence and adulthood using self-ratings of ADHD symptoms have reported lower heritability estimates (~0.30-0.50) (Michelini et al., 2015, Chang et al., 2013). However, these lower estimates may be due to rater effects and inflation of measurement error in self-ratings (captured in E influences within the individual-specific

environment), rather than to a lower contribution of genetic effects beyond childhood, as indicated by studies examining multiple raters (Larsson et al., 2013, Merwood et al., 2013). While most twin studies of ADHD have examined continuous ADHD symptoms in population-based samples (under the assumption that the risk for ADHD is normally distributed in the population), similar contributions of aetiological factors have been found for ADHD diagnosis measured as a present/absent category (Larsson et al., 2012).

1.2.3.2 Molecular genetic studies

A large number of molecular genetic studies have sought to pinpoint the common genetic variants (found in >5% of the population) contributing to the high heritability of ADHD (Thapar and Cooper, 2016). Prior to the development of genome-wide association (GWA) studies, molecular genetic research employed candidate genes and linkage approaches to examine the association between genetic variants associated with dopaminergic, noradrenergic and serotonergic systems implicated both in clinical response to drug treatment for ADHD (Faraone et al., 2005, Gizer et al., 2009). While replicated associations of several candidate genes have been reported (e.g., DRD4, DAT1, DRD5, 5HTT), a meta-analysis shows that effect sizes of each of these genes are very small, with odds ratios between 1.12 and 1.33 (Gizer et al., 2009). In addition, given the thousands of genetic variants in the genome, hypothesis-driven candidate gene and linkage approaches are prone to false positives (Kendler, 2013). An increased rate of large rare chromosomal mutations (frequent in <1% of the population), such as rare duplications and deletions termed copy number variants, have also been associated with ADHD, with larger effects (Williams et al., 2010).

More recent molecular genetic approaches have used hypothesis-free GWA approaches, testing for the association between ADHD and genetic markers across the whole genome (Neale et al., 2010). Until recently, GWA studies on ADHD in childhood had failed to detect single nucleotide polymorphisms (SNPs) below the stringent genome-wide significant threshold (p-value$<5\times10^{-8}$) (Neale et al., 2010, Hinney et al., 2011, Lasky-Su et al., 2010, Middeldorp et al., 2016, Neale et al., 2008, Mick et al., 2010). This failure highlights the need for collaborative efforts and larger samples including tens of thousands of cases and controls to accumulate sufficient power to detect significant associations. A new effort carried out by the Psychiatric Genetic Consortium (PGC), including over 20,000 cases and 35,000 controls, however, has recently identified the first 16 genome-wide significant loci for ADHD (Demontis et al., 2017). Given the complex genetic architecture of the disorder, with single genetic variants having very small effects, recent studies have also employed polygenic approaches and set out to aggregate the contribution of several

risk variants from GWA studies. These studies may be promising in guiding future research into the mechanisms underlying ADHD, and potentially the early prediction of individuals at greater genetic risk (Stergiakouli et al., 2016, Martin et al., 2015, Mooney et al., 2016).

1.2.3.3 Environmental risk

Several environmental risk factors have been associated with an increased risk for ADHD. The factors include maternal smoking, preterm birth, low birth weight, dietary factors, psychosocial factors and family adversity (Thapar et al., 2013). Most studies examining such environmental effects, however, have not controlled for unmeasured confounding familial risk factors shared between individuals living in the same family (Thapar and Rutter, 2009). As such, these associations do not necessarily reflect a role of the environmental factor per se, consistent with a causal effect, but could instead reflect effects of other background environmental or genetic risk factors that characterise families with ADHD. Quasi-experimental sibling-comparison studies have been employed to disentangle the effects of the environment and unmeasured confounds. The sibling-comparison approach compares siblings in the same pair to estimate environmental effects, while controlling for unmeasured confounding factors (i.e., genetic and environmental factors that make siblings similar, including risk factors associated with the investigated environmental factor). Studies using this approach have shown, for example, that the association of increased ADHD risk with maternal smoking during pregnancy, low SES, family adversity, and negative parenting may be due to unmeasured familial confounding, rather than a causal role of these environmental factors (Skoglund et al., 2014, Thapar and Cooper, 2016). The effect of other environmental factors, such as preterm birth, may instead be independent of familial confounding factors, and potentially causal (D'Onofrio et al., 2014).

1.2.3.4 Gene-environment interplay

Further research has examined the way that genetic and environmental factors may interact (Nigg et al., 2010, Thapar et al., 2013). Environmental risk factors, for example, may have an effect on a trait due to an interaction with an individual's genetic predisposition (gene-environment interaction), which makes an individual more susceptible to the effects of environmental influences (Nigg et al., 2010). Alternatively, an individual's genetic predisposition may increase the risk of exposure to certain environmental risks (gene-environment correlation) (Plomin, 2014). The interaction between genes and environmental factors has further been proposed as a possible reason for inconsistencies in candidate gene studies, as candidate genes may appear associated to the disorder only in the presence of certain environmental factors with which they interact (Buitelaar, 2005). A relatively limited amount of studies have examined

gene-environment interplay in ADHD, mostly focusing on dopaminergic and serotonergic neurotransmission genes (Stevens et al., 2009, Morgan et al., 2016, van der Meer et al., 2014), and effects have proven difficult to replicate (Nigg et al., 2010, Thapar et al., 2013, Gould et al., 2017). The environment may dynamically interact with an individual's genetic architecture via epigenetic processes, occurring when environmental or stochastic factors alter the expression of genes, without altering the DNA sequence (Mill and Petronis, 2008). Although research into the epigenetic mechanisms in ADHD is still in its infancy, initial data suggest a potential role of DNA methylation (an epigenetic mechanism commonly studied in psychiatric disorders) in genes related to neurodevelopmental processes in ADHD (Walton et al., 2017, van Mil et al., 2014).

1.2.4 Treatments for ADHD

The impairing nature of ADHD requires continued efforts to find efficient therapies and improve clinical outcomes for affected individuals. The National Institute for Health and Care Excellence (NICE) guidelines recommend pharmacotherapy as the first-line treatment for adults with ADHD and severe cases of ADHD in children and adolescents (Retz et al., 2011, Kendall et al., 2011, NICE, 2013). In milder childhood and adolescent cases, behavioural interventions (e.g., parental education, optimised classroom strategies, behavioural managed techniques) are preferred as first line of intervention (NICE, 2013).

Drug treatments for ADHD include stimulants (the most commonly prescribed medication treatment), such as methylphenidate and dexamphetamine, and non-stimulant drug treatments with atomoxetine, a noradrenaline reuptake inhibitor (NICE, 2013, Retz et al., 2011). Moderate-to-large effects of these medication treatments on ADHD symptoms and outcomes have been reported in a large body of research and meta-analyses in children (Prasad et al., 2013, Gayleard and Mychailyszyn, 2017, Chan et al., 2016, Maneeton et al., 2015) and adults (Maneeton et al., 2014, Faraone and Glatt, 2010, Meszaros et al., 2009). A recent meta-analysis, however, raised doubts on the efficacy and safety of stimulant medication for children with ADHD (Storebo et al., 2015), and led to an extensive debate amongst clinicians, with several authors considering the results of this study flawed (Mulder et al., 2016, Romanos et al., 2016, Banaschewski et al., 2016a, Banaschewski et al., 2016b).

Nevertheless, it is recognised that, in around one third of affected individuals with ADHD, medication may be ineffective, intolerable due to side effects, or unsuitable due to comorbid conditions (Biederman et al., 2004b). Among non-pharmacological treatments proposed as

alternatives to pharmacotherapy, the only interventions currently recommended by clinical guidelines are behavioural interventions (NICE, 2013). Yet, meta-analyses of randomised control studies indicate that, when outcome is rated by blinded reviewers, there are small-to-medium effects of behavioural interventions on childhood conduct problems and parenting (SMD=0.21-0.63), but non-significant effects on core symptoms of ADHD (Sonuga-Barke et al., 2013, Daley et al., 2014). A variety of other non-pharmacological interventions have been developed, such as neurofeedback, mindfulness training and cognitive training (Cortese et al., 2015, Cortese et al., 2016). Dietary interventions, such as free fatty acid supplementation, restricted elimination diets and artificial food colour exclusions, have also been investigated (Cooper et al., 2015, Nigg and Holton, 2014, Bloch and Mulqueen, 2014). Exercise interventions have also been recently proposed as alternative non-pharmacological options for ADHD, because of their potential for long-term, patient-led symptom management and reduction (Rommel et al., 2013, Halperin et al., 2014). However, strong evidence from blinded studies on the efficacy of available non-pharmacological treatments is still limited, and meta-analysis indicates significant, yet modest, effects only for free fatty acid supplementation and artificial food colour exclusion (Sonuga-Barke et al., 2013).

1.2.5 Summary

This section has provided an overview of ADHD as a clinical disorder, covering its epidemiology, aetiology and treatment options. Although the disorder was initially considered largely limited to childhood, decades of research have made it clear that ADHD can continue into adulthood, requiring further research applying a follow-up approach. High rates of comorbidities in adults, and the similar prevalence of ADHD in men and women, further highlight the need of more research into ADHD in adulthood in both genders. A focus on associated conditions may further help delineate adult ADHD from other common adult psychiatric conditions. Overall, ADHD is a highly complex disorder, with substantial heterogeneity among affected individuals in clinical symptoms, functional impairments and associated characteristics, which may, in turn, be associated with variability in treatment efficacy (Jeste et al., 2015).

1.3 Cognitive and neurophysiological impairments in ADHD

Cognitive and neurophysiological studies in ADHD seek to elucidate what are the mechanisms and processes that are associated with the symptoms and impairments of the disorder. The

identification of objective measures of alterations at the cognitive, neurophysiological and anatomical levels associated with the behavioural manifestations of ADHD may further our understanding of the pathways leading to the clinical features of the disorder. Investigating the impairments in cognitive and neural processes may further inform future research and clinical applications, and provide new targets for the development of new strategies of interventions, prevention and early identification of the disorder. Objective measures of cognitive and neural processes may be considered putative "biomarkers", defined as characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definition Working Group, 2001). In this section, I will provide an overview of the cognitive and neurophysiological methods used in this thesis, as well as review the previous studies on the cognitive and neurophysiological impairments associated with ADHD that are of particular relevance to this thesis.

1.3.1 Cognitive assessments and methods

Cognitive processes can be assessed with standardised cognitive instruments, such as IQ tests (Wechsler, 1991, Wechsler et al., 2008) and computerised cognitive tasks (Tamm et al., 2012, Nichols and Waschbusch, 2004). Performance on these assessments can provide information on an individual's cognitive abilities and impairments in the assessed cognitive domains. Cognitive tasks are largely based on measuring reaction time performance and accuracy. Mean reaction time (MRT) is assessed by averaging the latencies between stimulus appearance and participants' response (generally button click) over trials, and is often used as an index of processing speed. The standard deviation of response times can be captured by an index called reaction time variability (RTV), which gives an indication of the consistency of response times throughout a task. Task accuracy is generally examined by measuring the number of response omissions (omission errors [OE]) and incorrect responses (commission errors [CE]) to targets. OE are generally used as an index of ability to maintain attention over a period of time (sustained attention) and vigilance. CE are used to measure cognitive processes such as inhibitory control (ability to inhibit a prepotent response) and interference control (ability to control the interference due to competition of relevant and irrelevant stimuli).

A variety of cognitive and neuropsychological tasks have been employed to measure cognitive performance in ADHD. Several studies have focused on the continuous performance test (CPT), which requires participants to respond to a certain type of stimuli (target or "Go" stimuli) and

ignore distracting stimuli (non-target or "NoGo" stimuli) (Beck et al., 1956). CPT tasks are characterised by a low target probability, and probe sustained attention and vigilance. A similar cognitive task often used in ADHD research, the Go/NoGo task, includes Go and NoGo stimuli, but is characterised by a higher target probability compared to the CPT. Go/NoGo tasks are thus better at probing inhibitory control processes than standard CPT paradigms (Berwid et al., 2005). Another task often employed to study ADHD is the Eriksen flanker task (and its variants), measuring inhibitory control, performance monitoring and interference control processes, where targets are presented with congruent or incongruent flanking stimuli (Zhang, 1997). The cognitive-performance tasks used in this thesis are a CPT variant with cues preceding targets (Chapters 4 and 5), an arrow flanker task (Chapters 2, 3 and 4), and a simple four-choice reaction time task under slow-unrewarded baseline and faster-rewarded conditions (Chapters 4 and 6). More details on each task can be found in the respective chapters.

1.3.2 Cognitive impairments in ADHD

The study of cognitive impairments in ADHD is valuable to obtain a better understanding of the impairments in core processes associated with the disorder. Over the last few decades, it has become clear that ADHD is associated with several cognitive impairments compared with typically developing individuals, both in childhood and in adulthood. Cognitive deficits in ADHD encompass both executive, effortful cognitive functions (e.g., inhibitory control, working memory and sustained attention) and non-executive, more automatic cognitive processes (e.g., temporal information processing and timing, vigilance, intra-individual variability, choice impulsivity and reward processing) (Willcutt et al., 2005, Karalunas et al., 2014, van Lieshout et al., 2013, Mowinckel et al., 2015, Coghill et al., 2014, Mostert et al., 2015, Sonuga-Barke et al., 2010, Marco et al., 2009).

Executive dysfunction has been proposed to play a key role in ADHD since the earliest theoretical models of the disorder (Barkley, 1997, Barkley et al., 1992). Meta-analyses of cognitive studies in children with ADHD indicate moderate effects sizes (Cohen's d=0.43-0.69) for poorer performance on tasks measuring inhibition, short-term memory, working memory, sustained attention and planning (Willcutt et al., 2005, Huang-Pollock et al., 2012, Martinussen et al., 2005). Studies of adults reveal overall similar patterns of cognitive impairments (Hervey et al., 2004, Mowinckel et al., 2015, Lijffijt et al., 2005). Adults with ADHD have been found to show poorer performance compared to controls in Go/NoGo and CPT paradigms, with significantly more CE and OE, indicating impaired response inhibition and sustained attention, respectively

(McLoughlin et al., 2010, Woltering et al., 2013, Advokat et al., 2007, Boonstra et al., 2005). These group differences have been quantified in a meta-analysis of neuropsychological studies in adults with ADHD, indicating that significantly increased CE and OE have been reported in around 80% of studies, with medium effect sizes (Cohen's d=0.50-0.75) (Hervey et al., 2004).

ADHD is also strongly associated with increased RTV, capturing short-term fluctuations in response times thought to index lapses in attention (Karalunas et al., 2014, Kuntsi et al., 2010, Frazier-Wood et al., 2012). Evidence from meta-analyses and large studies consistently indicates moderate-to-large effect sizes for RTV impairments in children and adolescents with ADHD (Hedge's g and Cohen's d effect sizes between 0.72 and 0.85) (Kofler et al., 2013, Klein et al., 2006, Metin et al., 2012, Huang-Pollock et al., 2012) and a moderate effect size in adults (Hedge's g=0.46) (Kofler et al., 2013, Huang-Pollock et al., 2012). In ADHD, RTV has been identified as one of the best cognitive variables to distinguish between cases and controls (Klein et al., 2006), and showed the highest phenotypic and familial correlations with ADHD amongst several cognitive measures (Kuntsi et al., 2010). Meta-analytic evidence indicates more modest effects for increased MRT (d=0.37), measuring slower response speed (Huang-Pollock et al., 2012).

Lower IQ scores have further been consistently associated with ADHD, with meta-analytic estimates indicating an average difference between children with ADHD and controls of 7-11 points (Frazier et al., 2004). This finding is also supported by data from population samples, indicating moderate negative correlations of IQ with ADHD symptoms between -0.20 and -0.40 (Kuntsi et al., 2004, Rommel et al., 2015).

A potentially challenging aspect for cognitive studies in ADHD is whether to control for the effects of IQ when investigation the association between the disorder and other cognitive impairments (e.g., RTV). On the one hand, since IQ is associated with ADHD (Frazier et al., 2004), accounting for the effects of IQ could potentially remove part of the effects of interest (Miller and Chapman, 2001, Dennis et al., 2009). On the other hand, controlling for IQ allows to capture the association between ADHD and other variables beyond the association of ADHD with IQ (Dennis et al., 2009). An empirical approach, in the presence of differences between ADHD and control groups on IQ, is to conduct analyses both with and without including IQ as a covariate (Kuntsi et al., 2009, Rommelse et al., 2008a), or include IQ and other variables into multivariate analyses (Frazier-Wood et al., 2012). Both approaches are used in the studies included in the first part of this thesis (but not in the second part, as groups were matched on IQ). Previous

studies in children have shown that the relationship between ADHD and other cognitive impairments is largely not affected by covarying for IQ (Kuntsi et al., 2009, Rommelse et al., 2008a). Evidence from one of the largest cognitive-neurophysiological studies of ADHD in adolescence and young adults (also used for this thesis, Chapters 2-4), however, indicates that group differences may be reduced or disappear when controlling for IQ (Cheung et al., 2016, Kitsune et al., 2015). It has been further proposed that IQ may have a moderating effect on ADHD (Cheung et al., 2015, Cheung et al., 2016), as higher IQ has been associated with improved ADHD outcome (Gao et al., 2015, Agnew-Blais et al., 2016, Cheung et al., 2015, Cheung et al., 2016) and better ADHD medication response (Handen et al., 1997, Owens et al., 2003); although the former results has not been replicated in all available studies (Francx et al., 2015b, Breyer et al., 2014). Further evidence is needed to better understand the relationship between ADHD, IQ and other cognitive impairments in adolescents and young adults.

Overall, three decades of cognitive and neuropsychological research have shown that ADHD is associated with impairments in multiple cognitive domains. This evidence has contributed to a shift in the theoretical understanding of the disorder: from models that proposed one single deficit, for example in inhibition (Barkley, 1997, Barkley et al., 1992), underlying the multiple cognitive impairments, to more recent models that argue for multiple factors and pathways responsible for cognitive dysfunction in ADHD (Halperin and Schulz, 2006, Sonuga-Barke et al., 2010, Sergeant, 2005, Castellanos et al., 2006). Further research has aimed to clarify whether these impairments may reflect multiple underlying factors or a single core factor, as discussed more in detail in section 1.5.1.

1.3.3 Electrophysiological methods

While cognitive-performance measures can provide information on response times and accuracy during cognitive tasks, the measurement of brain activity during task performance enables a more direct investigation of overt and covert neurophysiological processes and brain functions underlying cognitive processes (Tye et al., 2011, Banaschewski and Brandeis, 2007, Luck et al., 2011). Among measures of brain function, neurophysiological measures of electrical activity derived from electroencephalography (EEG) enable a direct investigation of neural processes with millisecond temporal resolution (Banaschewski and Brandeis, 2007, Tye et al., 2011, McLoughlin et al., 2014a). EEG recordings are measured with electrodes placed on the scalp, which capture the electrical activity generated by groups of neurons synchronously firing to produce brain impulses (Buzsaki and Draguhn, 2004). Synchronised activity generates brain

rhythms (or oscillations), which are thought to represent the fundamental mechanism enabling the coordination of activity during brain functioning (Uhlhaas and Singer, 2006, Buzsaki and Draguhn, 2004). EEG data can measure spontaneous brain activity during resting state, indexing background processes such as arousal or activation, or brain responses evoked by particular stimuli during cognitive tasks, indexing a variety of cognitive processes such as attentional allocation and inhibition (Loo et al., 2015).

1.3.3.1 Traditional EEG approaches: quantitative EEG and event-related potentials

Raw EEG data consist of overlapping brain rhythms at different frequencies across power spectra, which represent the magnitude of power of brain activity. Through spectral decompositions, such as the Fast Fourier Transform (FFT), EEG activity can be divided into its constituent frequency bands (Figure 1.1), measured in cycles per second, i.e., hertz (Hz): delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (>30 Hz) (Schwilden, 2006, Loo and Makeig, 2012). The boundaries of these frequency bands are somewhat arbitrary and vary between studies. Yet the existence of different frequency bands is functionally meaningful, as different EEG rhythms have been shown to contribute to different aspects of neural processes: delta oscillations are predominantly associated with sleep and drowsiness; theta oscillations with arousal but also control and conflict cognitive processes; alpha oscillations with relaxation and attentive processes; beta oscillations with concentration and motor responses (Uhlhaas and Singer, 2006, Klimesch, 1999, Klimesch, 2012). Quantitative EEG (QEEG) analyses quantify the amount of power in each of these frequencies (Loo et al., 2015). These quantitative methods have been used to characterise changes in brain activity across development and alterations in psychiatric disorders (in contrast to earlier “qualitative” visual EEG inspections, still used in neurology). Although EEG can measure sub-second fluctuations, the temporal precision of EEG is not preserved in QEEG analyses, as these average the power within each frequency band over a continuous recording period (lasting at least a few minutes). As such, QEEG analyses are most useful for measuring brain processes in conditions where brain signals can be assumed to remain stable (i.e., stationary) over the measured recording period, such as resting state or sleep (Loo et al., 2015).

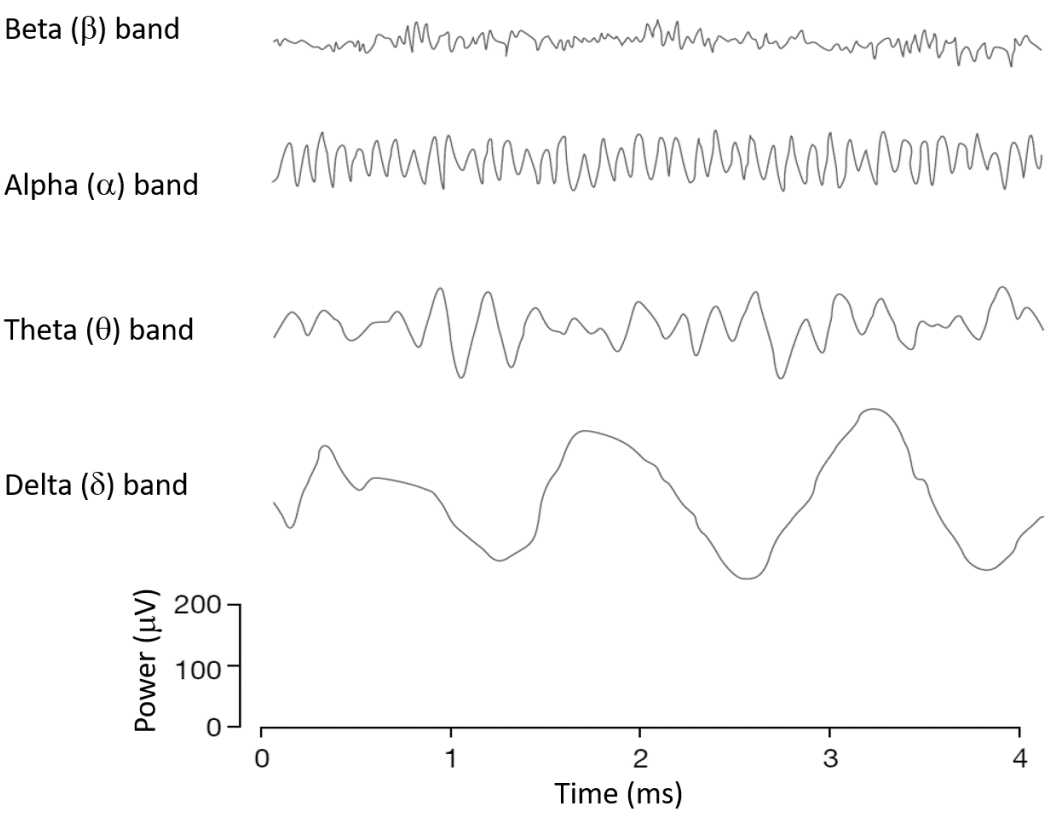

***Figure 1.1**. Typical EEG frequency bands. Adapted from Tye et al. (2011).*

While QEEG analyses do not capitalise on the excellent temporal resolution of EEG recordings, event-related potential (ERP) approaches measure sub-second increases in voltage that are time-locked to an event. An individual's ERP responses to the same stimulus in a task are typically averaged over a number of trials to produce an averaged ERP response. Averaging removes the background EEG oscillations unrelated to the stimulus (considered "noise", in traditional ERP approaches), and allows the emergence of the characteristic ERP waveform with alternating positive and negative peaks, termed ERP components (Figure 1.2) (Luck, 2014). ERP components are quantified by measuring their amplitude and latency, reflecting the magnitude and the timing of the allocated brain activity contributing to each component. Using cognitive paradigms such as Go/NoGo and CPT tasks, it is possible to elicit several ERP components and measure several overt and covert cognitive processes. A particular adaptation of the CPT, the cued CPT with flankers (or CPT-OX), has been used to characterise additional aspects of cognitive processes in ERP studies, allowing for the investigation of covert processes such as attentional orienting, response preparation and inhibition of a prepotent response (Banaschewski et al., 2003, van Leeuwen et al., 1998). In this adapted CPT, Cue stimuli precede both Go and NoGo stimuli, and participants are required to respond only when a Go follows the Cue, but to

withhold the response if the Cue is followed by a NoGo. Depending on the stimulus being presented, ERP components can reflect different processes. For example, the P3, a late positive enhancement observed after stimulus presentation (Polich and Kok, 1995, Polich, 2007), can index response inhibition when evoked by NoGo stimuli, response executions when evoked by Go stimuli, or attentional orienting when evoked by Cue stimuli.

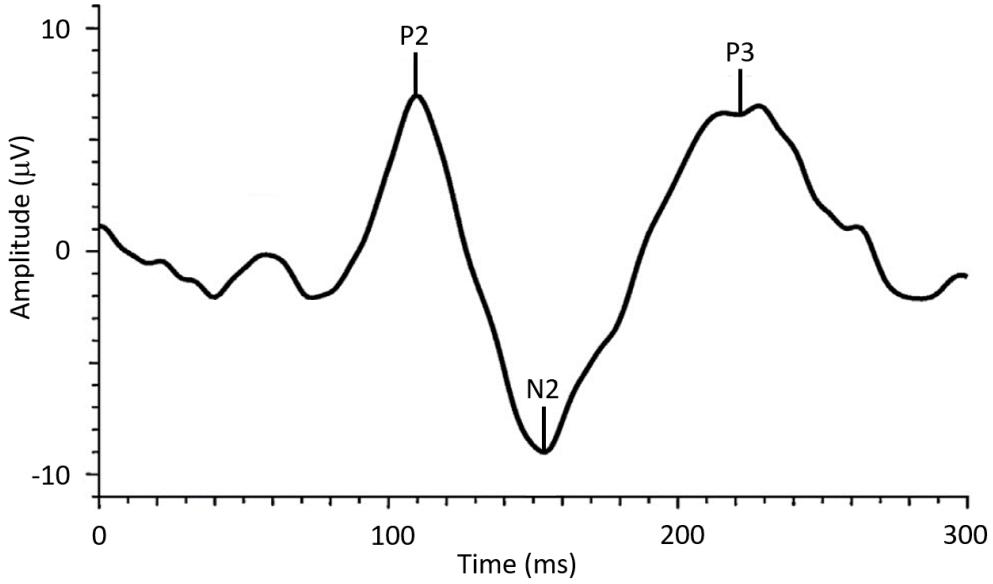

***Figure 1.2**. A typical ERP waveform showing characteristic positive and negative ERP components. Adapted from Odom et al. (2010).*

While ERPs preserve the information in the time domain, the averaged ERP responses do not provide information on the frequency bands underlying the measured brain potentials. Of note, ERP averages capture brain activity that is both time-locked and phase-locked to an event (i.e., evoked), but not activity that is time-locked but not phase-locked (i.e., induced) (Mazaheri and Picton, 2005, Schurmann and Basar, 2001). This means that the phase (e.g., positive or negative inclination) of an evoked response needs to align over trials for it to be reflected in the average ERP, while inconsistent phases across trials tend to be averaged out, producing attenuated or absent ERP peaks (Bickel et al., 2012). The averaged ERP amplitude may thus reflect a combination of power increases of the evoked response and of its phase consistency across trials (Basar-Eroglu et al., 1992, Spencer and Polich, 1999, Mazaheri and Picton, 2005).

1.3.3.2 Advanced EEG analyses: time-frequency and connectivity approaches

Although QEEG and ERP techniques are the most frequent approaches to analyse EEG activity in psychiatric conditions, they cannot fully capture the modulations of brain activity over time, with

combined characterisation of brain activity both in the frequency and time domain. More recent advances in signal processing, called time-frequency analyses, are able to combine the strengths of QEEG and ERP approaches, by allowing event-related time resolution of the EEG signal across the full power spectrum (Loo et al., 2015, Makeig et al., 2004a). These techniques measure changes of spectral power and phase that are time-locked to an event, and allow examination of sub-second modulations of brain oscillations at different frequency bands and at different temporal stages of stimulus processing (Makeig et al., 2004a, Pfurtscheller, 1981). Using similar cognitive paradigms as used in ERP studies, time-frequency analyses can quantify an event-related increase or decrease in power at each frequency over time, generally termed, respectively, event-related synchronisation (ERS) and event-related desynchronisation (ERD) or suppression (Bickel et al., 2012, Mazaheri and Picton, 2005). Additionally, indices of consistency of the phase of brain oscillations over trials can be extracted, to examine whether the processing of a stimulus repeated over time reflects stable or variable neural mechanisms (Makeig et al., 2004a, Papenberg et al., 2013). Greater phase consistency over trials is generally thought to reflect an adaptive mechanism to maintain stable neural processing of a stimulus (Makeig et al., 2004a, Papenberg et al., 2013). These approaches thus enable fine-grained modelling of EEG dynamics that cannot be captured by more traditional QEEG and ERP approaches.

Furthermore, advances in EEG analytic techniques have focused on ways to characterise the connectivity between brain signals at different brain regions, rather than the activity at single regions. Brain functional connectivity refers to the phenomenon of interdependence and communication between brain oscillations from different brain regions, measured with EEG or other neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) (Friston, 2011, Rubinov and Sporns, 2010). FMRI is an indirect measure of brain activity, as it measures magnetic changes associated with fluctuations in blood oxygen levels in areas of the brain (i.e., hemodynamic response). Although fMRI provides precise spatial resolution, it can only measure slow brain activity below 0.5 Hz (Lewis et al., 2016). As a consequence, fMRI connectivity methods are powerful in localising the patterns of connectivity between regions, but may only capture connectivity between slower brain oscillations. Instead, investigating brain connectivity using the excellent temporal resolution provided by EEG may allow to further capture transient changes in functional connectivity which underlie fast-changing cognitive processes (Coben et al., 2014, McLoughlin et al., 2014a, Silberstein et al., 2016).

A commonly used metric to characterise EEG connectivity is coherence, which measures the degree of cross-correlation in the time domain between oscillations at a given frequency

between pairs of EEG channels from different scalp regions (Barry et al., 2002, Nunez et al., 1997). However, since EEG activity measured at the scalp arises from the instantaneous projection, spreading and mixing of several underlying brain sources (i.e., volume conduction) (Onton and Makeig, 2006, Lopes da Silva, 2004, Nunez et al., 1997), EEG coherence between scalp channels may reflect inflated connectivity estimates. One effective way to measure connectivity between brain regions using scalp-level signals is to employ measures of functional association that capture interactions between brain signals not arising from artefacts of volume conduction with a certain phase lag, such as the imaginary part of the coherence (Nolte et al., 2004, Palva and Palva, 2012). Furthermore, recently-developed network approaches, such as those based on graph theory, may further be applied to better capture brain connectivity between several large-scale brain networks and identify connectivity alteration (Bullmore and Sporns, 2009, Rubinov and Sporns, 2010, Castellanos and Aoki, 2016).

Recent advances in EEG analyses further use statistical and computational approaches to measure the activity of brain sources, and their localisation and connectivity in the brain. Despite the excellent temporal resolution, EEG scalp distributions of traditional EEG methods result from several overlapping brain sources. As such, these traditional methods do not allow precise localisation of neural processes in the brain (McLoughlin et al., 2014a, Loo and Makeig, 2012, Makeig et al., 2004a). Advances in EEG approaches allow more precisely to investigate the patterns of cortical activation with enhanced spatial resolution (Makeig et al., 1997, McLoughlin et al., 2014a). Recently developed analysis techniques, such as independent-component analysis (ICA), are able to isolate individual sources of EEG activity, thus providing improved spatial resolution compared to standard EEG techniques. Performing connectivity analyses on these source-activities, rather than scalp-based measures, may thus enable the investigation of connectivity between more localised functional networks, and tracking of the dynamic formation of functional networks during cognitive processes (Loo et al., 2015).

1.3.4 EEG impairments in ADHD

1.3.4.1 QEEG studies

Using EEG methods, several studies have shown atypical brain activity during resting states and task performance in ADHD (Tye et al., 2011, Loo and Makeig, 2012). QEEG abnormalities have been found both in children and adults with the disorder (Tye et al., 2012, Loo et al., 2009, Loo et al., 2010, Kitsune et al., 2015). In particular, individuals with ADHD show increased power in the lower frequency bands (delta and theta) and decreased power in the faster frequency bands

(alpha and beta), during resting state (Tye et al., 2012, Loo et al., 2009, Loo et al., 2010, Kitsune et al., 2015, Dupuy et al., 2013, Snyder and Hall, 2006). Further evidence indicates that very low frequency activity (<0.5 Hz), thought to represent a marker of the default-mode network (DMN), may be decreased in children and adults with ADHD at rest (Helps et al., 2008, Helps et al., 2010). Additionally, previous evidence has shown an imbalance in slow and fast EEG rhythms (indicated by increased theta/beta ratio) in individuals with ADHD, with an effect size of 3.08 and sensitivity and specificity of 94% in a meta-analysis of QEEG studies in ADHD (Snyder and Hall, 2006). These large effects led to the approval by the Federal Drug Administration (FDA) in the USA of the theta/beta ratio as an aid in ADHD diagnosis in combination with standard diagnostic tools (Snyder et al., 2015, Stein et al., 2016). Several more recent studies, however, have not reported alterations in theta/beta ratio in ADHD (Rommel et al., 2016, Arns et al., 2016, Loo et al., 2013, Skirrow et al., 2015), indicating inconsistent evidence for the use of the theta/beta ratio as a putative biomarker for the disorder (Arns et al., 2013, Arns et al., 2016, Loo et al., 2013, Saad et al., 2015). Further studies have examined QEEG profiles in individuals with ADHD during simple cognitive tasks, such as the CPT, but several inconsistencies across studies have emerged. For example, increased, decreased and intact alpha power have each been reported in different studies (Loo et al., 2009, Nazari et al., 2011, Skirrow et al., 2015, Rommel et al., 2016). Overall, despite early reports of certain QEEG indices (theta/beta ratio) as promising biomarkers for the disorder, these results may indicate a need for better EEG biomarkers for ADHD.

1.3.4.2 ERP studies

Previous studies have shown patterns of atypical ERP activity underlying multiple cognitive processes, such as attentional allocation, inhibition, motor response preparation and performance monitoring, in individuals with ADHD (Albrecht et al., 2013, Geburek et al., 2013, Cheung et al., 2016). Evidence of impaired attentional and inhibitory processing in ADHD is supported by ERP studies reporting attenuations of ERP components differentiating ADHD probands from controls. Several studies of children, adolescents and adults with ADHD have found, using CPT and Go/NoGo tasks, a reduced fronto-central P3 component in response to NoGo stimuli (NoGo-P3), reflecting atypical response inhibition (Albrecht et al., 2013, Banaschewski et al., 2003, Doehnert et al., 2013, McLoughlin et al., 2010, McLoughlin et al., 2011, Groom et al., 2010b). In addition, attenuations in the parietal P3 (Cue-P3) and central contingent-negative variation (CNV) in response to Cue stimuli have been reported in individuals with ADHD using the CPT-OX paradigm, indicating deficits in attentional orienting and response preparation, respectively (McLoughlin et al., 2010, Banaschewski et al., 2004, Doehnert et al., 2013). Attenuated P3s to target stimuli, reflecting allocation of attentional resources for

response execution, have also been reported in children, adolescents and adults with ADHD (Banaschewski et al., 2004, Groom et al., 2010b, Cheung et al., 2017, Grane et al., 2016), as confirmed by a meta-analysis (Szuromi et al., 2011). Yet, intact target P3s in ADHD have also been found (Groom et al., 2008, McLoughlin et al., 2010, Barry et al., 2009, Albrecht et al., 2013), which may indicate potentially context-dependent impairments in the target P3 measured with different cognitive tasks.

Alterations in ERPs of performance monitoring, indicating the cognitive ability in goal-directed behaviour to monitor ongoing performance and to adjust response selection, have also been found in individuals with ADHD. Reduced frontal N2 components, reflecting conflict monitoring processes arising from two competing responses and evaluation of the correct response, have been found during flanker tasks in children and adults with ADHD (McLoughlin et al., 2009, Albrecht et al., 2008, Wild-Wall et al., 2009), although not in all studies (Johnstone and Galletta, 2013, Jonkman et al., 2007). N2 attenuations have further been reported in ADHD using the Stop Signal Task and Go/NoGo tasks (Woltering et al., 2013, Pliszka et al., 2000), but generally not in CPT-OX tasks (McLoughlin et al., 2010, Doehnert et al., 2013, McLoughlin et al., 2011, Albrecht et al., 2013), indicating that impairments may be limited to paradigms inducing higher conflict monitoring demands (McLoughlin et al., 2009, Barry et al., 2009, McLoughlin et al., 2014b). Further impairments in performance-monitoring ERPs in individuals with ADHD have been reported in components underlying error processing when an incorrect behavioural response is made (Geburek et al., 2013). In particular, the fronto-central error-related negativity (ERN), reflecting automatic error processing, has been found reduced in children and adults with ADHD during flanker tasks (Albrecht et al., 2008, McLoughlin et al., 2009) and Go/NoGo tasks (Groom et al., 2013), as also indicated by a meta-analysis showing medium effect sizes (Cohen's d=0.50) (Geburek et al., 2013). ERN reductions, however, have not been found in all studies, for example using Go/NoGo tasks (Wiersema et al., 2009, Groom et al., 2010a, O'Connell et al., 2009). Similarly, mixed evidence exists on reductions in the error-related positivity (Pe), reflecting more conscious error processing, which have been found in some studies (O'Connell et al., 2009, Wiersema et al., 2009, Groom et al., 2013), but not in others (Albrecht et al., 2008, McLoughlin et al., 2009). Some of the inconsistencies across studies on ERPs of performance monitoring may be partly attributed to variability across studies in the way these components are measured (e.g., with peak amplitude or area amplitude approaches), and most studies have used modest sample sizes. Larger-scale investigations remain rare to date, but are needed to help clarify the extent to which these ERPs are impaired in ADHD.

1.3.4.3 Time-frequency studies

More recent studies have also examined the synchronisation/desynchronisation of power and variability of phase of EEG oscillations during cognitive tasks with time-frequency approaches. Available evidence indicates that children and adolescents with ADHD show reductions in phase consistency of target- (McLoughlin et al., 2014b) and response-locked theta activity (Groom et al., 2010a), and in alpha ERD following targets (Lenartowicz et al., 2014) and cue stimuli preceding targets (Mazaheri et al., 2014). Evidence in adults further suggests reductions in cue- and target-related alpha and beta ERDs (Hasler et al., 2016). These results indicate that individuals with ADHD may be characterised by suboptimal ability to maintain a consistent pattern in the timing of evoked theta response over trials (theta phase variability) (McLoughlin et al., 2014b, Groom et al., 2010a), as well as in attentional mechanisms related to attentional selection (target-related alpha ERD), sensory gating (cue-related alpha ERD) and motor preparation and execution (cue- and target-related beta ERD). A recent time-frequency study on EEG oscillations during a working memory task found reduced alpha ERD during encoding, and increased theta ERS and alpha ERS during maintenance of the stimulus in children with ADHD compared to controls (Lenartowicz et al., 2014). Increased power in the latter two measures in individuals with ADHD may reflect mechanisms aimed at compensating for the deficits in alpha ERD in the earlier encoding stage of the task. Combined, these three indices predicted ADHD status with 70% accuracy (Lenartowicz et al., 2014). Taken together, available time-frequency studies in ADHD indicate impairments in measures that can capture fine-grained modulations in brain activity. The investigation of brain-oscillatory indices underlying various stages of cognitive processes with time-frequency analyses may help a deeper investigation into the alterations in neural processes implicated in ADHD (Loo et al., 2015). Yet, compared with ERP studies, considerably fewer studies have examined brain activity during cognitive performance in ADHD with time-frequency approaches.

1.3.4.4 EEG connectivity studies

Further evidence on neurophysiological alterations in ADHD comes from studies investigating impairments in functional connectivity. During resting state, EEG studies examining coherence values between EEG channels have shown mixed evidence of hypo- and hyper-connectivity in slower and faster brain oscillations between different cortical regions. Several studies have reported increased intra- and inter-hemispheric coherence in children with ADHD (Clarke et al., 2007, Dupuy et al., 2008, Barry et al., 2005), especially in slow frequency bands (delta, theta) (Barry et al., 2002, Clarke et al., 2005, Clarke et al., 2007). Reduced coherence values, however, have also been reported, in particular in the alpha and beta bands (Barry et al., 2002, Barry et

al., 2005, Clarke et al., 2005). Fewer studies have examined adults with ADHD during resting states. Available evidence suggests increased connectivity in delta coherence (Barttfeld et al., 2014), no differences in theta coherence, but lower coherences in the alpha band (Clarke et al., 2008) in adults with ADHD compared to controls.

Studies examining brain connectivity in ADHD during task performance, which may allow a more direct examination of alterations underlying impairments in cognition and behaviour (Ernst et al., 2015, Finn et al., 2017), have similarly reported inconsistent results. For example, previous studies have indicated that connectivity may be reduced in children with ADHD (Mazaheri et al., 2010, Mazaheri et al., 2014), while other studies have found increased connectivity in the alpha (Murias et al., 2007) and beta (Silberstein et al., 2016) bands. No study to date has examined EEG connectivity during task performance in adults.

Overall, available studies to date indicate several connectivity alterations in individuals with ADHD. This evidence is in keeping with atypical functional connectivity profiles reported with other neuroimaging techniques, in particular fMRI. Yet, although both increased and decreased connectivity have been reported with EEG, a large number of fMRI studies reported decreased connectivity during resting states, especially within the DMN and between the DMN and networks that become more active during a task performance (e.g., the executive control network) in children and adults with ADHD (Fair et al., 2010, Sripada et al., 2014, Sun et al., 2012, Castellanos et al., 2008, Uddin et al., 2008). Patterns of increased resting-state connectivity between or within these networks, however, have also been reported (Barbera et al., 2015, Hoekzema et al., 2014, McCarthy et al., 2013, Tian et al., 2006, Sidlauskaite et al., 2016). Task-based fMRI studies have shown hypo-connectivity in fronto-striato-cerebellar networks during sustained attention (Rubia et al., 2009) and inhibition (van Rooij et al., 2015a, Cubillo et al., 2010, Vloet et al., 2010), and hyper-connectivity within the DMN (van Rooij et al., 2015a) and between networks of reward/cognitive control integration. The inconsistencies in results from EEG and fMRI studies may be due to the different methodological strengths of these techniques (outlined above in section 1.3.3). EEG methods are particularly indicated for studying transient and fast-changing neural processes underlying the cognitive impairments implicated in ADHD, as they allow a more precise characterisation of deficits at multiple sensory and cognitive processing stages with sub-second temporal resolution (Makeig et al., 2004a, McLoughlin et al., 2014a). In addition, the majority of EEG connectivity studies conducted to date in ADHD present methodological limitations, such as the use of connectivity metrics contaminated by volume-conduction artefacts, which may produce inaccurate connectivity profiles.

1.3.5 Summary

Overall, the studies reviewed in this section indicate that ADHD is associated with several alterations in cognitive processes and brain activity measured by EEG, both during resting state and during task performance. While other neuroimaging modalities are not the focus of this thesis and are not reviewed in detail, studies on cognitive functions and EEG activity are largely consistent with impairments in wide-spread neural processes in ADHD reported with other neuroimaging techniques. For example, fMRI studies indicate that individuals with ADHD show alterations across partially separate neural networks, which include the frontal-parietal network, the DMN and the ventral-attentional network, involved in executive but also non-executive cognitive processes (Cortese et al., 2012, Castellanos and Proal, 2012). Although several studies have investigated abnormalities in cognitive function and brain activity in children, adolescents and adults, fewer studies have investigated the developmental and aetiological pathways of these alterations in individuals with ADHD.

1.4 Developmental trajectories of cognitive-neurophysiological impairments in ADHD

1.4.1 Continuity of impairments from childhood to adulthood

While cross-sectional studies are suggestive of similar impairments in cognitive and brain functions across development, prospective longitudinal studies with repeated assessments of ADHD and cognitive measures are needed to establish developmental patterns. Longitudinal research to date has mostly focused on higher-level cognitive functions (e.g., working memory, organisation, response inhibition), with several studies showing that impairments tend to persist from childhood to adolescence and adulthood in ADHD persisters (Cheung et al., 2016, Biederman et al., 2009, Hinshaw et al., 2007). This pattern is also observed for IQ (Cheung et al., 2016, Biederman et al., 2009). Fewer prospective longitudinal studies have investigated the developmental association between ADHD and lower-level cognitive impairments, such as intra-individual variability measured with RTV. The three largest studies conducted to date on RTV have shown persisting impairments both from middle to late childhood (Vaughn et al., 2011), and from childhood to adolescence/early adulthood in ADHD persisters compared to neurotypical individuals (Thissen et al., 2014, Cheung et al., 2016); although in one of these

studies the impairment did not persist in their oldest group of adults aged 22 or above (Thissen et al., 2014). Further studies have investigated the continuity of cognitive impairments in ADHD, but comparability to the above findings is less clear due to reliance on small samples or not making a distinction between individuals with persistent ADHD and remitted ADHD at follow-up (Doehnert et al., 2013, Moffitt et al., 2015). Studies not differentiating between remitters and persisters have found that deficits in visual processing, vigilance, inhibition and IQ may continue in adult age (Moffitt et al., 2015). For RTV, measured with different tasks, continuity of impairments was observed from childhood to adulthood in a smaller-scale study (Doehnert et al., 2013), but ADHD-control differences were less clear in adolescence (Doehnert et al., 2010). In another longitudinal study, some cognitive impairments (response inhibition) persisted in adolescence in ADHD persisters, while others did not (RTV, working memory) (McAuley et al., 2014); yet comparability of the latter study to other studies is not clear, as different control groups were used in childhood and adolescence.

Overall, studies to date converge in indicating that most cognitive impairments persist when ADHD persists from childhood to later assessments. Yet, most studies in adulthood have used samples of young adults, and studies with assessments of older age groups are needed to fully characterise the developmental trajectories of ADHD-related impairments across the lifespan. With regard to studies examining impairments in brain function in ADHD, little data exist as yet, but an initial prospective longitudinal EEG study reported that, among impairments in Cue-P3, NoGo-P3 and CNV observed in childhood, only deficits in the CNV were associated with ADHD in adults (n=11) (Doehnert et al., 2013). However, within this small-scale study, it was not possible to differentiate between persistent and remitted ADHD at follow-up. Further longitudinal EEG studies are needed to better understand the developmental continuity of such deficits.

1.4.2 Predictors of ADHD outcome

The prediction of later ADHD outcome (persistence/remission), within ADHD samples, based on early (childhood) impairments in cognition and brain function may be important for early identification of those at risk for worse long-term outcomes (van Lieshout et al., 2013). Studies examining such longitudinal prediction within childhood only, when ADHD symptoms have persisted in all individuals, indicate that impairments in early childhood in executive functions, especially inhibition and working memory, and in IQ predicted ADHD symptoms in later childhood (Berlin et al., 2003, Campbell and von Stauffenberg, 2009, Kalff et al., 2002, Brocki et al., 2007), whereas RTV was not predictive (Vaughn et al., 2011). Studies investigating clinical

outcomes of ADHD persistence/remittance, with follow-up assessments in adolescence and adulthood, have obtained inconsistent results. Recent studies suggest that RTV and working memory in childhood may predict ADHD symptoms and/or functional impairment in adolescents and young adults (van Lieshout et al., 2016a, Sjowall et al., 2015), even when controlling for childhood ADHD symptoms (Sjowall et al., 2015). This is inconsistent with results of studies examining later outcome as persistence/remission, which found no evidence for association of aggregated measures of executive functions, sustained attention, inhibition, working memory and RTV in childhood and ADHD remission/persistence in adolescence and adulthood (Biederman et al., 2009, Mick et al., 2011, Cheung et al., 2015). In a recent follow-up study, IQ was the only cognitive measure in childhood which predicted later ADHD remission/persistence, while measures of attention, inhibition, working memory and RTV did not predict future ADHD status (Cheung et al., 2015). The predictive value of IQ has been replicated in two other samples of young adults (Agnew-Blais et al., 2016, Gao et al., 2015), but not in other studies (Francx et al., 2015b, Breyer et al., 2014). The only study to date to examine the predictive value of brain activity in childhood on ADHD adult outcome indicate that resting-state EEG measures in the theta and beta bands in childhood predict adult ADHD remission/persistence (Clarke et al., 2011), especially in frontal regions which are implicated in ADHD.

Overall, these studies suggest that, while some cognitive impairments in children with ADHD may predict levels of ADHD symptoms at short term (within childhood and when symptoms of ADHD persist in all individuals), results are more mixed for predictions into adolescence and adulthood. Further research, also including measures of brain activity along with cognitive measures, is needed to elucidate what neurocognitive impairments are the most predictive in terms of ADHD persistence.

1.4.3 Markers of remission and enduring deficits

The identification of cognitive and neural processes underlying the trajectories of persistence and recovery from childhood-onset ADHD during the transition to adulthood may further contribute to the prevention of negative long-term outcomes. It has been hypothesised that the persistence of ADHD from childhood to adulthood would be predicted by the degree of maturation and improvement over time in higher-level cognitive function (Halperin and Schulz, 2006). Contrary to this compensatory mechanism, lower-level cognitive functions would be linked to the presence of ADHD in childhood irrespective of later clinical status (Halperin and Schulz, 2006). In a follow-up study of almost 100 individuals with childhood ADHD assessed with

both cognitive function and EEG activity, ADHD remitters did not differ from controls in higher-level cognitive functions (e.g., working memory and inhibition), but were still impaired in measures associated with lower-level cognitive processes (e.g., RTV) and movement level (Halperin et al., 2008). These results were supported by a second study on the same sample, where RTV did not distinguish ADHD remitters from persisters, both of whom were impaired compared to controls (Bedard et al., 2010).

Other studies, however, have not found an association between ADHD remission and improvements in higher-level cognitive functions. Three studies reported that ADHD remitters and persisters in adolescence and adulthood did not differ from one another, and were both impaired compared to neurotypical individuals, in an aggregate index of executive functions (Biederman et al., 2009), interference control (Pazvantoglu et al., 2012), and response inhibition (McAuley et al., 2014). Working memory impairments in young adults diagnosed with ADHD in adolescence compared to controls were also observed regardless of whether they still met an ADHD diagnosis (Roman-Urrestarazu et al., 2016). Two recent studies (on one of the samples used for this thesis; Chapters 2-4) further found, across different cognitive tasks, that cognitive-EEG measures of preparation, intra-individual variability and vigilance (mostly reflecting lower-level cognitive functions) differentiated ADHD remitters from persisters assessed in adolescence and young adulthood (James et al., 2017, Cheung et al., 2016). Instead, cognitive and brain activity measures of executive control of inhibition and working memory (reflecting higher-level cognitive functions) were not sensitive to persistence/remission of the disorder (Cheung et al., 2016). As such, these studies may suggest that cognitive processes and brain activity of preparation-vigilance ("lower-level") processes – instead of higher-lever functions – may be markers of ADHD remission, following the symptom level at follow-up.

Only three studies have examined the developmental pathways of brain connectivity in individuals with a diagnosis of ADHD in childhood, using fMRI. Two of these studies suggest that lower functional correlation between posterior cingulate and medial prefrontal cortices (major components of the DMN) during rest (Mattfeld et al., 2014) and lower connectivity between the thalamus and prefrontal regions during response preparation (Clerkin et al., 2013) may distinguish ADHD persisters from remitters and controls. Resting-state medial-dorsolateral functional associations in the prefrontal cortex, implicated in cognitive control, may instead be reduced in both ADHD remitters and persisters, compared to controls (Mattfeld et al., 2014), potentially indexing an enduring deficit. A recent larger-scale study further reported increased

resting-state fMRI connectivity in ADHD remitters compared to controls in the executive control network, with intermediate connectivity profiles in persisters (Francx et al., 2015a).

Overall, despite some inconsistencies between studies, initial convergence across cognitive and neurophysiological markers of ADHD persistence and remittance is starting to emerge. For example, ADHD remitters show both reduced RTV and increased DMN activity compared to persisters (James et al., 2017, Cheung et al., 2016, Mattfeld et al., 2014). This corresponds to the hypothesis of an association between intra-individual variability and the DMN in ADHD (Sonuga-Barke and Castellanos, 2007), which may both represent markers of remission. In addition, most studies to date show that impairments in executive functions do not distinguish ADHD remitters and persisters (Biederman et al., 2009, McAuley et al., 2014, Roman-Urrestarazu et al., 2016, Pazvantoglu et al., 2012, Cheung et al., 2016). Future studies should aim to address the inconsistencies across studies using methodologically robust procedures. One possible reason for some of the discrepancies across studies may be found in the way the persistence and remission are defined. While ADHD diagnosis in childhood is commonly based on parent-report assessments, studies differ in the use of parent- or self-reports at later assessments. However, there is a relatively low agreement between self- and parent-reports of ADHD in adolescents and young adults, and recent evidence shows that objective cognitive and neurophysiological data show lower agreement with ADHD outcome based on self-reports than on parent-reports (Du Rietz et al., 2016). Future studies should also consider more explicitly how the follow-up data on cognitive-neurophysiological markers relate to baseline data on cognitive and brain function.

1.4.4 Summary

The studies reviewed in this section show that cognitive and neurophysiological impairments tend to persist into adulthood in individuals with persistent ADHD. Instead, when ADHD remits in the transition to adulthood, there appears to be a separation between measures that may represent markers of remission, distinguishing persisters from remitters at follow-up, and measures that are not sensitive to ADHD outcome. Most studies, however, have used cognitive-performance measures, and studies examining the association between measures of brain activity and ADHD outcomes remain limited. It also remains unclear how aetiological factors related to ADHD map onto the trajectories of neurocognitive and brain function alterations. Future longitudinal and clinical studies are needed to address these questions.

1.5 Aetiological overlap between cognitive-neurophysiological impairments and ADHD

One possible explanation for the phenotypic association between cognitive-neurophysiological impairments and ADHD is that the same genes contributing to ADHD may also account for impairments in the cognitive and neural processes. Genes associated with ADHD may be non-specific, but pleiotropic, meaning that each gene may influence more than one trait or disorder, either co-occurring at the same time or manifest at different times across development (Kovas and Plomin, 2006, Thapar and Cooper, 2016).

It has been proposed that alterations in cognitive and neural processes in psychiatric disorders may lay on the causal pathway between the genetic susceptibility and the phenotypic expression of the disorder (Doyle et al., 2005, Castellanos and Tannock, 2002). From this perspective, cognitive and neural indices have been employed in psychiatric genetic research with an "endophenotype" approach, as possible targets (alternative to more heterogeneous behavioural presentations to which the endophenotypes are associated) to facilitate the discovery of genetic variants for psychiatric diagnoses (Almasy and Blangero, 2001, Castellanos and Tannock, 2002, Gottesman and Gould, 2003, Doyle et al., 2005, Waldman, 2005). The construct of endophenotype (also commonly known as "intermediate phenotype") refers to a measurable trait, mediating between the genetic susceptibility to a certain disease and its phenotypic expression (Gottesman and Shields, 1973, Gottesman and Gould, 2003). Limited evidence, however, has emerged that the aetiology of intermediate phenotypes may be considerably simpler than that of psychiatric diseases (Flint and Munafo, 2007). Early endophenotype models may thus have been based on overly simplistic models of gene action, also ignoring the role of environmental influences and the interplay with gene expression (Loo et al., 2015). In addition, most endophenotype studies do not clearly discriminate between a "liability-index" (or "risk indicator") model and a "mediational" model (Kendler and Neale, 2010). The liability-index model specifies that a common set of genes increases the risk for both the putative intermediate phenotype and the disorder, implying pleiotropy. The mediational model makes the stronger assumption that the causal pathway from a set of genetic variants to a psychiatric disorder would pass exclusively through the associated marker. Kendler and Neale (2010) have proposed that the term endophenotype should be applied only to variables satisfying the mediational model, whilst variables fitting the liability-index model should be considered biomarkers.

Nevertheless, the study of the overlap in aetiological factors between ADHD and cognitive-neurophysiological impairments can help improve our understanding of the mechanisms underlying the disorder. This section will provide an overview of quantitative genetic studies of the association between cognitive-neurophysiological impairments and ADHD.

1.5.1 Quantitative genetic studies of cognitive impairments in ADHD

Cognitive impairments in ADHD have been investigated in several family studies, showing that unaffected first-degree family members (e.g., siblings) of children with ADHD may show the same cognitive impairments found in affected probands in their family (Rommelse et al., 2008b, Andreou et al., 2007, Sonuga-Barke et al., 2010, Loo et al., 2008, van Rooij et al., 2015b, von Rhein et al., 2015). This similarity in cognitive impairments is attributable to familial factors (genetic and environmental influences shared between ADHD probands and their affected and unaffected family members).

In the presence of a phenotypic association between ADHD and a cognitive or neurophysiological measure, sibling and twin model-fitting studies are able to decompose this association into contribution of aetiological factors (familial and non-familial factors in sibling studies; genetic, shared environmental and non-shared environmental factors in twin studies) (see section 1.2.3.1 above). The overlap in the aetiological influences between two traits is further estimated with correlational indices. For example, genetic and familial correlations estimate the degree of overlap in genetic and familial influences, respectively, between two given traits (Kuntsi et al., 2010, Rijsdijk and Sham, 2002). Sibling and twin model-fitting studies in childhood have found substantial overlap between familial/genetic influences on ADHD and on several cognitive impairments, including IQ, working memory, inhibition, RTV, timing and delay aversion (Andreou et al., 2007, Frazier-Wood et al., 2012, Kuntsi et al., 2010, Wood et al., 2010, Wood et al., 2011). Several twin studies have sought to quantify the degree of genetic overlap underlying the phenotypic association between ADHD symptoms and IQ. One study in children aged 5 years old found a genetic correlation (r_A) of -0.45 between IQ and ADHD symptoms (on a continuum), and of -0.59 with ADHD diagnosis (present/absent) (Kuntsi et al., 2004). The shared genetic influences accounted for 86% and 100% of the phenotypic association of low IQ with, respectively, ADHD symptoms and diagnosed ADHD (r=-0.28/-0.34, respectively) (Kuntsi et al., 2004). Similar estimates have been reported in more recent twin studies on general populations (Wood et al., 2010, Greven et al., 2014, Polderman et al., 2006). Using a

longitudinal twin model, another study has further shown that the genetic factors underlying the developmental association between ADHD and IQ at age 12, 14 and 16 are largely stable over time, yet some time-specific genetic influences also emerge on ADHD, IQ and their association at 14 and 16 years (Rommel et al., 2015). Similarly, twin studies have estimated that the phenotypic association between RTV and ADHD symptoms is moderately-to-largely explained by genetic factors, with estimates of genetic correlation between 0.31 and 0.64 (Kuntsi et al., 2014, Cheung et al., 2014, McLoughlin et al., 2014b). Less consistent evidence exists for a genetic overlap between ADHD symptoms and measures of inhibition and working memory. Using a composite of ratings of ADHD symptoms from parents and teachers, a study found low, non-significant genetic correlations between CE and both ADHD symptom domains (r_A=0.11 with inattention and r_A=0.17 with hyperactivity-impulsivity) (Kuntsi et al., 2014).

Quantitative genetic research has further focused on whether the multiple impairments associated with ADHD may reflect a multifactorial structure or a single core impairment. Using a multivariate familial factor analysis approach, one study found two separable familial factors accounting for cognitive impairment in a large sample of children and adolescents with ADHD, unaffected siblings and control sibling pairs (Kuntsi et al., 2010). The first, larger factor, accounting for 85% of the familial variance of ADHD, captured 98% and 100% of the familial variance of MRT and RTV, respectively. The second, smaller factor, accounting for 13% of the familial variance of ADHD, captured 62% and 82% of the familial variance of CE and OE, respectively (Kuntsi et al., 2010). These results have been interpreted as reflecting a dissociation between the aetiological influences underlying largely bottom-up (RTV) and top-down (response accuracy) processes in ADHD (Kuntsi et al., 2010). A subsequent study, using a similar approach in ADHD and control sibling pairs assessed with a different large neuropsychological battery, found a similar two-factor structure (Frazier-Wood et al., 2012). The first factor explained 100% of the familial influences on an aggregated measure of intra-individual variability and 50% of the familial influences of ADHD. The second factor captured 100% of the variance of digit-span backwards (measuring working memory) and a small proportion of the variance of ADHD (15%), Stop Signal RT (speed of the inhibition process) (20%), and IQ (33%) (Frazier-Wood et al., 2012). The majority of the familial influences on Stop Signal RT and IQ remained unaccounted for by the model, suggesting a partial separation from the other two factors. Taken together, these studies suggest the presence of two partially independent familial processes, one capturing increased intra-individual variability, and the other factor capturing impairments in executive function, such as response accuracy and working memory (Frazier-Wood et al., 2012, Kuntsi et al., 2010). The aetiological separation of RTV from response accuracy was also confirmed in a

more recent twin study on a population sample, where RTV showed a substantial genetic overlap with inattentive symptoms (r_A=0.64) but no significant genetic overlap with CE (r_A=-0.10) (Kuntsi et al., 2014). IQ may further potentially represent a third factor, as also indicated by three other twin and sibling studies showing that the genetic/familial influences shared between IQ and ADHD are largely separate from those shared between other cognitive impairments and the disorder (Wood et al., 2010, Wood et al., 2011, Rommelse et al., 2008c). The evidence of multiple aetiological factors is reflected in more recent theoretical models, which propose multiple processes and pathways underlying neurocognitive dysfunctions in ADHD (Halperin and Schulz, 2006, Sonuga-Barke et al., 2010, Sergeant, 2005, Castellanos et al., 2006, Johnson, 2012). Yet, results differ between studies on the number of factors that may underlie ADHD, likely owing to different tasks and varying (and often limited) number of measures included. In addition, limited evidence exists on the aetiological factor structure of cognitive impairments in ADHD in adolescence and adulthood, which is the focus on one of the studies included in this thesis (Chapter 4).

1.5.2 Quantitative genetic studies of neurophysiological impairments in ADHD

Electrophysiological alterations are moderately-to-highly heritable. A meta-analysis of twin studies of electrophysiological measures (Van Beijsterveldt and Van Baal, 2002) and a more recent systematic review (de Geus, 2010) indicate that genetic factors account for 60-90% and for 40-80%, respectively, of the variance of QEEG and ERP measures. Environmental factors also seem to play a role via the non-shared route (Zietsch et al., 2007, Stroganova et al., 2009, Gilmore et al., 2010).

Family studies on samples including individuals with ADHD have shown that unaffected first-degree family members of ADHD probands show some degree of impairment (scores typically between affected probands and controls) in ERP measures of inhibitory control (NoGo-P3), attentional allocation and orienting (Cue-P3), response preparation (CNV), conflict monitoring (N2) and error processing (ERN), both in children and adolescents (Albrecht et al., 2008, Albrecht et al., 2010, Albrecht et al., 2013) and in adults (McLoughlin et al., 2009, McLoughlin et al., 2011). Although this evidence suggests shared familial effects, less than a handful of quantitative genetic studies have quantified the contribution of genetic factors underlying the observed association between EEG measures and ADHD. The three available studies, using a modest sample of adolescent twins from the general population selected for having high and low ADHD symptoms (n=134; 30 MZ or DZ pairs concordant or discordant for high ADHD symptom scores,

and 37 MZ or DZ pairs concordant for low ADHD symptom scores), found moderate-to-large genetic overlap of ADHD symptoms with elevated theta power during rest (r_A=0.35) (Tye et al., 2014), reduced very-low frequency power during the CPT-OX (r_A=0.80) (Tye et al., 2012) and increased source (ICA)-based frontal midline theta phase variability during an arrow flanker task (r_A=0.51) (McLoughlin et al., 2014b). In the latter study, theta phase variability further showed a substantial genetic overlap with RTV. Yet, these studies focused more on the significance of the association between measures and ADHD (measured with t and p-value statistics on the difference between high- and low-ADHD symptom groups on the EEG measures), rather than on the size of these associations with standardised statistics. As such, limited conclusions can be derived from the evidence of genetic overlap between ADHD and the investigated EEG markers on the proportion of phenotypic association explained by shared genetic factors.

1.5.3 Summary

Investigating cognitive impairments and EEG alterations in individuals with ADHD can provide an important tool to gain a better understanding of the mechanisms that are impaired in the disorder. By further exploring the aetiological architecture of the observed associations between ADHD and cognitive-EEG impairments, available studies further indicate that familial/genetic influences largely underlie such associations, although studies remain limited and more research is warranted, especially on EEG indices. The use of multivariate approaches may be particularly valuable in this regard, both to clarify the aetiological overlap between ADHD and cognitive-neurophysiological impairments, but also to investigate the shared aetiology between impairments in cognitive functions and in brain activity. Ultimately, a better understanding of the aetiology and pathophysiology of ADHD will lead to improved causal modes of the disorder, as well as more refined targets for intervention.

1.6 Bipolar disorder and comparison with ADHD

Bipolar disorder (BD) denotes a severe psychiatric condition generally occurring in adulthood. Although diagnostic classifications consider it distinct from ADHD (APA, 2013), the two disorders present certain areas of symptomatic overlap. In some cases, this overlap can lead to uncertainties regarding diagnostic boundaries between these two disorders, which can have negative consequences in terms of incorrect diagnostic and treatment decisions.

1.6.1 Clinical symptoms and epidemiology of BD

BD has been classified under the DSM category of mood disorders until the DSM-IV-TR edition (APA, 2000). In the DSM-5, BD has been classified separately from depressive disorders, to recognise the commonalities in terms of aetiology, family history and symptomatology with depressive disorders but also schizophrenia (APA, 2013). Individuals with BD may experience unusually intense emotional states that occur for distinct periods of time in episodes of mania and depression. A manic episode is a period lasting at least one week (or any duration if hospitalisation is necessary) of abnormally elated, expansive or irritable mood, increased talkativeness, impulsiveness, distractibility, activity, grandiose ideation and decreased need for sleep. A depressive episode is a period of at least two weeks of persistent and pervasive low mood and/or a loss of interest, pleasure or energy, along with difficulty concentrating, psychomotor retardation, increased need for sleep and suicidal ideation (APA, 2013, APA, 2000). Psychotic symptoms may also occur during manic and depressive states, such as hallucinations and delusional beliefs. Between episodes, individuals return to periods of relatively normal mood (euthymia), although full functioning may not be reached (Muller-Oerlinghausen et al., 2002, Henry et al., 2013). The DSM-IV-TR and DSM-5 include different types of BD (APA, 2013, APA, 2000), which may be considered on a "bipolar spectrum" (Alloy and Abramson, 2010). BD type I (BD-I) is defined by the presence of one or more manic episodes or mixed episodes of mania and depression which may be alternated with depressive episodes. BD type II (BD-II) is characterised by at least one depressive episode and at least one hypomanic episode (similar to a manic episode, but less severe and impairing) lasting at least four days, but no full-blown manic or mixed episodes. Finally, cyclothymia is considered a milder but more chronic form of BD, defined by hypomanic episodes alternated to episodes of mild or moderate depression, less severe than full-blown depressive episodes (APA, 2013, APA, 2000).

BD is conceptualised as a disorder of adult age, with onset in late adolescence or early adulthood. The lifetime prevalence of BD is estimated at around 1-3.9% (Merikangas et al., 2011, Fajutrao et al., 2009, Kessler et al., 2005, Merikangas et al., 2007). BD-I is the most common form of BD, with prevalence ranging between 0.6% and 2.2%. Equal proportions of men and women are affected by BD. In a large study on adults from 11 countries, higher lifetime prevalence of BD-I was found in males that females, while greater prevalence of BD-II was found in females (Merikangas et al., 2011). Around three-quarters of individuals with BD present with a co-occurring or lifetime psychiatric disorder, such as anxiety (60% of BD cases), substance use disorder (40%), ADHD (20%) or conduct disorder (20%) (Merikangas et al., 2011). Comorbidities

may be more frequent in men than in women (Hendrick et al., 2000). BD is highly heritable, with heritability estimates ranging between 0.58 and 0.77 (Song et al., 2015, Edvardsen et al., 2008, Barnett and Smoller, 2009, Smoller and Finn, 2003); since the aetiology of BD is not a specific focus of this thesis, relevant literature will not be discussed in detail.

1.6.2 Cognitive and neurophysiological impairments in BD

BD is associated with impairments in multiple cognitive domains. Meta-analytic evidence indicates that several executive functions, such as sustained attention, working memory and inhibition, are impaired in BD, with medium-to-large effect sizes during depressive and manic episodes (Cohen's d=0.55-1.43) (Kurtz and Gerraty, 2009). Of note, these impairments tend to persist during euthymia (Robinson et al., 2006), with medium-to-large effect sizes (d=0.61-0.83) (Kurtz and Gerraty, 2009). For example, impairments in response inhibition and sustained attention have been found in individuals with BD during Go/NoGo and CPT paradigms, as indicated by higher numbers of CE and OE (Clark et al., 2002, Torres et al., 2007, Robinson et al., 2013). Increased RTV has further been reported during CPT tasks (Brotman et al., 2009, Bora et al., 2006, Moss et al., 2016). Impairments in executive functions have also been found in individuals before BD onset in longitudinal studies, suggesting that such impairments in BD are state-independent (Meyer et al., 2004, Ratheesh et al., 2013). Atypical profiles in executive functions and in RTV have also been reported in first-degree family members of individuals with BD (Adleman et al., 2014, Brotman et al., 2009, Erol et al., 2014, Kulkarni et al., 2010). This evidence suggests that familial influences may underlie the association of such impairments with BD.

EEG studies of BD have shown alterations in QEEG profiles and ERP components. Resting-state theta and delta power may be increased in individuals with BD, while alpha power may be decreased (Basar and Guntekin, 2013, Outhred et al., 2014). Individuals with BD may show a pre-attentive dysfunction, indexed by abnormalities in early sensory and attentional ERP components, such as reduced mismatch negativity (MMN) and P50, in auditory tasks (Hall et al., 2007, Cabranes et al., 2013, Jahshan et al., 2012). P3 components have been studied in BD individuals mostly in comparison to individuals with schizophrenia using oddball paradigms, to examine target discrimination and stimulus context updating (Chun et al., 2013, Maekawa et al., 2013, Thaker, 2008, Polich, 2007). Reduced target P3 amplitudes in individuals with BD compared to controls have been shown during auditory oddball paradigms (Ethridge et al., 2015, Bersani et al., 2015, Kaur et al., 2011) and using a task with standard, deviant and target

conditions (Maekawa et al., 2013). P3 attenuations have further been reported in first-degree unaffected relatives of individuals with BD (Pierson et al., 2000), indicating familial influences on this ERP component. Normal enhancements of the P3 component to target stimuli, however, have also been found using a visual three-stimulus oddball paradigm (Bestelmeyer, 2012), an auditory oddball paradigm (Schulze et al., 2008) and a Go/NoGo task (Chun et al., 2013). Previous studies also suggest impairments in BD in P2 and fronto-central P3 component (also called P3a), thought to reflect stimulus classification and covert attentional orienting, respectively (Ethridge et al., 2015, Jahshan et al., 2012). Reduced CNV amplitudes have further been reported in BD, indicating attentional deficits of response preparation (Li et al., 2015). Studies examining ERPs of performance monitoring have found conflicting results. Two studies on participants with BD found reduced N2 amplitude in response to target stimuli with an auditory oddball paradigm (Ethridge et al., 2012, Ethridge et al., 2015). Another study, however, found no N2 reductions in individuals with the disorder (Morsel et al., 2014). Two recent studies examining ERPs of error processing found evidence of significantly reduced ERN (Morsel et al., 2014), suggestive evidence of increased ERN and significantly reduced Pe (Kopf et al., 2015). The use of small samples in most ERP studies of BD may explain some of the inconsistencies in results, and warrants further empirical data. Initial evidence from studies using time-frequency approaches further suggests that individuals with BD show increased event-related beta and delta power (Ozerdem et al., 2008b, Ozerdem et al., 2008a, Tan et al., 2016, Ethridge et al., 2012, Ethridge et al., 2015), and decreased theta and alpha power (Atagun et al., 2013, Basar et al., 2012, Ethridge et al., 2012, Ethridge et al., 2015) during visual and auditory oddball tasks compared to controls. Yet, these studies used time-frequency methods applied on averaged ERP (evoked) responses, rather than more sophisticated time-frequency decompositions capturing both evoked and induced increases and decreases in brain oscillations. Further research is needed to provide full characterisation of event-related oscillatory responses in BD.

1.6.3 Comparison between BD and ADHD

1.6.3.1 Similarities and differences in clinical characteristics

Diagnostic formulations for ADHD and BD present certain areas of symptomatic overlap. Adult ADHD may present with some symptoms common to manic episodes, such as distractibility, psychomotor restlessness and talkativeness (Kent and Craddock, 2003, Skirrow et al., 2012, Asherson et al., 2014). The ceaseless distractible and uncontrolled thought processes and wandering mind (everyday thoughts flitting from one topic to another) seen in many adults with ADHD may be similar to racing thoughts or flight of ideas typical of mania (Asherson, 2005,

Asherson et al., 2014). Additionally, both disorders may be characterised by features of mood dysregulation, such as irritability and emotional lability (Skirrow and Asherson, 2013, Skirrow et al., 2012). However, although mood dysregulation is commonly seen in patients with ADHD and patients with BD, it is not disorder-specific, but instead typical also of other psychiatric conditions often co-occurring with ADHD and BD, such as major depressive disorder and anxiety disorders (Cumyn et al., 2009, Skirrow and Asherson, 2013). These symptomatic similarities may result in uncertainty regarding the boundaries of the two disorders, and difficulties in distinguishing between the two disorders when patients are referred for first clinical assessments (Skirrow et al., 2012, Asherson et al., 2014). Diagnosis influences treatment decisions, which differ for the two disorders (typically stimulants or atomoxetine for ADHD, and mood stabilisers or antipsychotics for BD), making the correct distinction between ADHD and BD critically important (Skirrow et al., 2012, Asherson et al., 2014). Under the DSM-5, the delineation between the two disorders may be further complicated by the inclusion of mood dysregulation as an associated feature of ADHD, and of persistently increased goal-directed energy and activity as a symptom of BD (APA, 2013).

In addition, ADHD and BD often co-occur (Merikangas et al., 2011, Hensch et al., 2011, Klassen et al., 2010). This co-occurrence may be partly explained by shared familial/genetic factors. Meta-analytic evidence summarising results of family studies has shown that there is an increased prevalence of ADHD among family members of individuals with BD (relative risk [RR]=2.6) and an increased prevalence of BD among relatives of individuals with ADHD (RR=1.8) (Faraone et al., 2012). Genetic studies using GWA approaches have further confirmed this aetiological overlap between ADHD and BD, showing that shared common genetic variants are associated with a range of psychiatric disorders, including ADHD and BD (Lee et al., 2013). A recent meta-analytic GWA study also found a substantial SNP-based genetic correlation between ADHD and BD (r_A=0.64) (van Hulzen et al., 2016).

Despite wide areas of overlap between ADHD and BD, there are clinical characteristics that are not common between the two disorders. For example, the elated mood and grandiosity observed during manic episodes, and the psychomotor retardation, loss of energy and suicidal ideation typical of depressive episodes, are not part of ADHD symptoms (Asherson et al., 2014). Another important difference in clinical presentations between ADHD and BD is that, while ADHD symptoms are chronic, trait-like and represent differences from developmental norms, BD symptoms tend to occur for a distinct period and refer to changes from an individual's usual euthymic state (APA, 2000, APA, 2013). Yet, although BD diagnosis requires episodicity of

symptoms, it has been shown that individuals with BD between episodes still show residual symptoms of distractibility and mood dysregulation (overlapping with ADHD) and impairments in functional performance (Henry et al., 2013). In addition, while relatively clear alterations of episodes is seen in BD-I and BD-II, these are less distinct in cyclothymia, which represents a more chronic form of BD (Skirrow et al., 2012).

Only few small-scale studies have directly examined the suitability of standard diagnostic tools to distinguish between ADHD and BD. One study found that individuals with ADHD (n=16) and individuals with BD (n=15) showed increased scores on a depression scale relative to controls (Torralva et al., 2011). In another study, scores on an ADHD rating scale were able to discriminate between ADHD and BD, but individuals with BD during euthymia showed lower levels of depressive and manic symptoms than individuals with ADHD (Ibanez et al., 2012). In a more recent study from one of the samples used for this thesis (Chapters 5 and 6), ADHD interview measures and self-ratings of ADHD symptoms best discriminated between women with ADHD and women with BD, while measures of emotional lability and depressive symptoms were increased in both groups relative to control women (Kitsune et al., 2016).

1.6.3.2 Similarities and differences in cognitive and neurophysiological impairments

Comparative studies across ADHD and BD, using cognitive and EEG measures, may aid in the distinction of impairments that are shared and may potentially underlie the overlap in symptoms between ADHD and BD, from impairments that may be distinct between the two disorders. The latter group of measures has the potential to help identify objective measures which could serve as biomarkers to aid in distinguishing between the two conditions.

Although previous research has shown evidence of similar cognitive impairments in attentional and inhibitory processing in ADHD and BD separately, only a few cognitive studies have directly compared these processes in adults with ADHD or BD, concluding that subtle differences in executive function impairments may aid in distinguishing between the disorders (Levent et al., 2014, Torralva et al., 2011). One study used an extensive neuropsychological battery measuring multiple cognitive domains (short-term, verbal, non-verbal, logical and working memory, attention, various other executive functions including motor inhibitory control). This study found that ADHD and BD groups could not be distinguished based on their performance on attention, inhibition, short-term and working memory, but that individuals with ADHD performed better in verbal and non-verbal memory tests (Torralva et al., 2011). Another study assessed ADHD and BD groups on a digit span test, a verbal memory test, the Wisconsin Card

Sorting Test and Stroop Test, and found that individuals with BD showed poorer performance than individuals with ADHD in all tests except for inhibitory control measured with the Stroop Test (Levent et al., 2014). Yet, participants with ADHD only showed differences from controls on the Stroop Test, but not in other tasks, suggesting that the ADHD group may have been less impaired than samples used in other studies.

Similarly, only a few small-scale studies have examined the similarities and differences between ADHD and BD on neurophysiological impairments. One study on 12 adults with ADHD and 13 adults with BD investigating ERP measures of reward processing using a gambling task found significant impairments in the amplitude of a reward-sensitive P3 in both clinical groups compared to controls (n=25) (Ibanez et al., 2012). Yet, similar to controls, individuals in the BD groups displayed an increase in P3 amplitude with increasing reward magnitude, while individuals with ADHD showed no modulation of the P3 with reward magnitude changes. In a recent QEEG study from one of the samples used for this thesis (Chapters 5 and 6), both women with ADHD (n=20) and women with BD (n=20) showed increased theta power during rest compared to controls (n=20) (Rommel et al., 2016). Both groups further lacked an increase in theta power (observed in controls) in switching from rest to the CPT-OX task, but no differences emerged between clinical and control groups during the task. Another study assessed resting-state brain functional connectivity and temporal variability in connectivity in the delta band in a small sample of adults with euthymic BD (n=11) and with ADHD (n=9) relative to healthy controls (n=15) (Barttfeld et al., 2014). Results suggest that delta connectivity was increased in both clinical groups, while connectivity variability was increased in ADHD but reduced in BD compared to controls. Finally, two studies, of which only one included a control sample (Nazhvani et al., 2013), used a machine learning approach to classify individuals with ADHD or BD based on their resting-state EEG power and early visual ERP (P1) (Nazhvani et al., 2013, Sadatnezhad et al., 2010). Both resting-state EEG power data, and P1 amplitude and latency data combined, yielded a high classification accuracy, of 72-87% and 93%, respectively. Overall, empirical data from cross-disorder cognitive-neurophysiological studies of ADHD and BD are limited to date. In particular, little is known on the differences or similarities in cognitive and brain processes that are relevant to the behavioural symptoms that overlap between ADHD and BD, such as distractibility or impulsivity. No published study prior to this thesis has compared impairments in attentional and inhibitory processes in ADHD and BD in adulthood using ERP or time-frequency EEG measures. In addition, most EEG studies, especially on ADHD, have been performed on male samples, and very little is known about these processes in females. Further studies are needed, to compare cognitive-neurophysiological markers between ADHD and BD

and gain further insights into distinct and overlapping impairments. The identification of disorder-specific objective measures would further our understanding of impairments associated with ADHD and BD, and potentially assist in differentiating between the two disorders.

1.6.4 Summary

This section has introduced the clinical, cognitive and neurophysiological features of BD, and provided an overview of similarities and differences from ADHD. The clinical manifestations of BD present certain areas of overlap with that of ADHD. The two disorders may also often co-occur. The overlap between BD and ADHD may be challenging in clinical settings when an individual presents with symptoms such as distractibility, emotional lability, restlessness, which characterise both disorders. Assigning a correct diagnosis is necessary to make correct treatment decisions, as different treatments are indicated for the two disorders. Careful clinical considerations are required to delineate between ADHD and BD, and may benefit from the development of biomarkers to aid in diagnostic decisions and treatment monitoring. Cross-disorder comparisons between ADHD and BD on measures of neurocognitive and brain function may point to measures that could represent such candidate biomarkers. Studies examining ADHD and BD separately suggest that similar but also distinct cognitive-neurophysiological impairments may characterise the two disorders. However, very few direct cross-disorder comparison studies have been carried out to date, and more research is warranted to confirm the extent to which cognitive and neurophysiological profiles may help differentiate between the two disorders.

1.7 Aims and objectives

This thesis uses a multi-disciplinary approach to study cognitive and neurophysiological impairments underlying ADHD in adolescence and adulthood. The first part (Chapters 2, 3 and 4) aims to further our understanding of the developmental pathways and aetiological structure of these impairments in adolescents and young adults with a childhood diagnosis of ADHD-C, their unaffected siblings and age-matched neurotypical participants. The second part of this thesis (Chapters 5 and 6) aims to compare cognitive-neurophysiological profiles between women with ADHD, women with BD and control women, in order to identify impairments that are specific to, or shared between, ADHD and BD. Overall, by using a combination of cognitive,

neurophysiological, developmental and sibling-modelling approaches, this work aims to further our understanding of the developmental pathways, aetiology and specificity of cognitive impairments and brain activity alterations in adolescents and adults with ADHD.

1.7.1 Part 1: developmental and aetiological pathways to ADHD (Chapters 2, 3 and 4)

ADHD persists into adolescence and adulthood, either in full or in partial remission, in the majority of children clinically diagnosed in childhood (Faraone et al., 2006). Yet, the mechanisms underlying persistence and remission are poorly understood.

Chapters 2 and 3 aim to extend previous research into the cognitive and EEG markers of ADHD remission and enduring deficits (reviewed in section 1.4.3), by examining, for the first time, the association of ADHD outcomes with ERPs of performance monitoring (Chapter 2) and EEG functional connectivity measures (Chapter 3) in a follow-up study of individuals with ADHD-C in childhood. Chapter 2 examines profiles of cognitive and ERP impairments of performance monitoring (N2, ERN, Pe components) in ADHD persisters, remitters and controls, as well as the continuous association between these cognitive-ERP measures and ADHD severity within the childhood ADHD group. Chapter 3 represents a further investigation into the neurophysiological impairments of ADHD with advanced EEG connectivity methods, to extend our understanding into functional connectivity in adolescents and adults with ADHD during a cognitive control task, as well as to examine the association of the identified connectivity markers with persistent and remitted ADHD.

Chapter 4 investigates the aetiological mechanisms underlying persistent ADHD, by examining the aetiological factor structure of cognitive and ERP impairments associated with persistent ADHD in adolescence and young adulthood in Chapter 2 and previous studies (Cheung et al., 2016, Cheung et al., 2017). Specifically, this chapter aims to estimate the extent to which the impairments in cognitive-ERP measures in ADHD cluster into one or more familial and non-familial factors.

1.7.2 Part 2: comparison between ADHD and BD (Chapters 5 and 6)

ADHD and BD in adults present certain areas of symptom overlap, which in some cases may lead to incorrect clinical decisions. Direct cognitive-neurophysiological comparisons between ADHD and BD are limited to date, but may reveal disorder-specific impairments in the two disorders.

Chapter 5 compares cognitive-performance and ERP measures of attentional and inhibitory processes from the CPT-OX task in a sample of women with ADHD, women with BD and control women. Chapter 6 further examines RTV and alterations in brain activity of attentional processes in the three groups, extracted with ERP and time-frequency analyses, during the Fast task, a four-choice RT task with baseline and fast-incentive conditions. Both studies use an all-female sample, in order to match the groups on gender but also to explore the neglected area of EEG indices associated with these processes in females, especially in ADHD samples.

CHAPTER 2 - Attention-deficit/hyperactivity disorder remission is linked to better neurophysiological error detection and attention-vigilance processes

Archival Report

Biological Psychiatry

Attention-Deficit/Hyperactivity Disorder Remission Is Linked to Better Neurophysiological Error Detection and Attention-Vigilance Processes

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ABSTRACT

BACKGROUND: The processes underlying persistence and remission of attention-deficit/hyperactivity disorder (ADHD) are poorly understood. We examined whether cognitive and neurophysiological impairments on a performance-monitoring task distinguish between ADHD persisters and remitters.

METHODS: On average 6 years after initial assessment, 110 adolescents and young adults with childhood ADHD (87 persisters, 23 remitters) and 169 age-matched control participants were compared on cognitive-performance measures and event-related potentials of conflict monitoring (N2) and error processing (error-related negativity and positivity) from an arrow flanker task with low-conflict and high-conflict conditions. ADHD outcome was examined with parent-reported symptoms and functional impairment measures using a categorical (DSM-IV) and a dimensional approach.

RESULTS: ADHD persisters were impaired compared with controls on all cognitive-performance and event-related potential measures (all $p < .05$). ADHD remitters differed from persisters and were indistinguishable from control participants on the number of congruent (low-conflict) errors, reaction time variability, error-related negativity, and error-related positivity (all $p \leq .05$). Remitters did not differ significantly from the other groups on incongruent (high-conflict) errors, mean reaction time, and N2. In dimensional analyses on all participants with childhood ADHD, ADHD symptoms and functional impairment at follow-up were significantly correlated with congruent errors, reaction time variability, and error-related positivity ($r = .19–.23$, $p \leq .05$).

CONCLUSIONS: Cognitive and neurophysiological measures of attention-vigilance and error detection distinguished ADHD remitters from persisters. These results extend our previous findings with other tasks and indicate that such measures are markers of remission and candidates for the development of nonpharmacological interventions.

Keywords: ADHD, Cognitive impairments, EEG, Event-related potentials, Persistence, Remission

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The identification of cognitive and neural processes underlying the trajectories of persistence and recovery from childhood-onset disorders during the transition to adulthood has the potential to prevent negative long-term outcomes (1,2). Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5%–6% of children and adolescents worldwide (3,4). ADHD often persists into adulthood, where the prevalence rate is around 2%–3% (5), with severe impacts on many aspects of individuals' lives (6,7). Although in a proportion of cases ADHD symptoms reduce to subclinical levels from childhood to adulthood (8), little is known about the compensatory processes and enduring deficits of ADHD.

It has been proposed that the cognitive processes associated with persistence of ADHD across development may be separate from those linked to the remission of the disorder (9). However, empirical data to date are inconsistent with regard to the exact pattern of cognitive impairments that distinguish ADHD remitters from persisters. Whereas some studies comparing ADHD remitters and persisters have linked remission to better executive function performance (1,10), other studies have found no differences between ADHD remitters and persisters in adolescence and adulthood on measures of executive functions (11–15).

The assessment of neurocognitive processes using cognitive and brain activity data may allow a deeper understanding of the developmental trajectories of ADHD. Our recent investigation of adolescents and young adults with childhood ADHD assessed on a range of cognitive, event-related potential (ERP), and electroencephalography (EEG) measures found that ADHD remitters differed from persisters, but not from control participants, on preparation-vigilance measures (reaction time variability [RTV], omission errors, ERP activity of response preparation, and delta and theta activity) and actigraphic data on movement. Executive-function processes

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of inhibition and working memory (commission errors, digit span backward, and ERP activity of inhibitory control), instead, were not sensitive to ADHD persistence or remission, as ADHD remitters showed an intermediate pattern between persisters and control participants, without significant differences from either group (14). Further combined investigations of cognitive and neurophysiological data may aid our understanding of the mechanisms underlying ADHD remission and persistence.

Neurocognitive impairments in ADHD include deficits in performance monitoring, an essential cognitive ability in goal-directed behavior to monitor ongoing performance and to adjust response selection (16–18). The investigation of performance-monitoring impairments with ERP parameters, including the N2 and the error-related negativity (ERN) and positivity (Pe), in individuals with ADHD may provide new information to elucidate the neurocognitive pathways of remission. The N2 is a frontocentral stimulus-locked negative deflection mostly observed 200–400 ms after the presentation of stimuli inducing high conflict (such as incongruent stimuli) and when a correct response is made (17,19). This ERP reflects a conflict-monitoring process, as it results from the conflict arising from two competing responses and evaluation of the correct response (19). When a participant makes an error, the ERN, a frontocentral response-locked negative deflection at around 0–150 ms is observed, followed by the Pe, a centroparietal positive enhancement at around 200–400 ms after response (20–22). The ERN is thought to reflect unconscious activity of a generic response-monitoring system immediately after a mistake is made, whereas the Pe is thought to represent conscious error processing to adjust response strategy (23).

In ADHD, N2 attenuation in the flanker task has been reported in children and adults with ADHD (24–26), although two smaller studies failed to replicate this finding (27,28). With regard to ERN and Pe attenuation in ADHD, a recent meta-analysis found an overall ERN attenuation in performance-monitoring tasks (29). Pe attenuations in ADHD samples were significant in Go/NoGo tasks, but not flanker tasks. Yet, data on these ERPs in individuals with ADHD are overall limited, and study samples have remained small. Furthermore, studies have not, to date, investigated the association between neurophysiological performance monitoring and ADHD persistence and remission. One recent study showed that ERN and Pe deficits may be improved with motivational incentives or methylphenidate medication in ADHD groups (30), suggesting malleability of the error-processing impairments in ADHD.

In the present study, we aimed to extend our recent findings (14) by investigating cognitive and neurophysiological impairments from a performance monitoring task in adolescents and young adults with persistent and remitted ADHD. We examined ADHD outcome with parent-reported symptoms and functional impairment measures using both a categorical (DSM-IV) and a dimensional approach. Based on our previous results and evidence of potentially malleable neurophysiological error processing, we predicted that cognitive measures underlying nonexecutive processes and ERPs of error processing (ERN/Pe) would distinguish between ADHD persisters and remitters and would represent markers of remission. We further predicted that cognitive indices of executive control would not vary with persistence or remission of ADHD. No formal predictions were made for ERP measures of conflict monitoring (N2), owing to absence of any evidence suggesting a possible association with remission or persistence of ADHD.

METHODS AND MATERIALS

Sample

The sample consists of 279 participants, who were followed up on average 5.8 years (SD = 1.1) after initial assessments: 110 had a diagnosis of DSM-IV combined-type ADHD in childhood (10 sibling pairs and 90 singletons) and 169 were control participants (76 sibling pairs and 17 singletons) (14,31). Participants with ADHD were initially recruited from specialized ADHD clinics (32) and control participants from schools in the United Kingdom. Information on any diagnosed neurodevelopmental and psychiatric conditions and medication use were collected through neuropsychiatric screening. Exclusion criteria at both assessments included IQ < 70, autism, epilepsy, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. Other comorbidities were not excluded in order to have an ADHD sample that is representative of the clinical population. At follow-up, we excluded six control participants who met DSM-IV ADHD criteria based on the parent-reported Barkley Informant Rating Scale (33) and six participants with ADHD who had missing parent ratings of clinical impairments. Two participants with childhood ADHD, who did not meet ADHD symptom criteria but met clinical levels of impairment at follow-up, were also excluded to minimize heterogeneity in the sample.

Among those with childhood ADHD, 87 (79%) continued to meet clinical (DSM-IV) levels of ADHD symptoms and impairment (ADHD "persisters"), whereas 23 (21%) were below the clinical cut-off (ADHD "remitters") (31). Among ADHD remitters, 14 displayed ≥5 items on either the inattention or hyperactivity/impulsivity symptom domains, but they did not show functional impairment. ADHD persisters, remitters, and control participants did not differ in age, but there were significantly more male participants in the remitted group than in the other two groups, with no female participants among ADHD remitters (Table 1). Participants attended a single research session for clinical, IQ, and cognitive-EEG assessments. Almost one-half (47%) of the participants with childhood ADHD were being treated with stimulant medication at follow-up. Those who were on medication scored significantly higher on ADHD symptoms ($F = 11.34$, $p < .01$) and functional impairment ($F = 5.22$, $p < .01$) than those who were not taking medication. However, the proportion of participants on medication did not differ between ADHD persisters and remitters ($\chi^2 = 1.95$, $p = .16$). A 48-hour ADHD medication-free period was required prior to assessments. Three ADHD persisters (3.4%) were also on antidepressant medication, but for ethical reasons they were not asked to stop taking them. These participants were included in all analyses as their exclusion did not alter the results. Parents of all participants gave informed consent following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

Table 1. Sample Demographics Divided by Group, With Test for Group Differences

					ADHD-P vs. Ctrl	ADHD-P vs. ADHD-R	ADHD-R vs Ctrl
	ADHD-P	ADHD-R	Ctrl	*p*	*p*	*p*	*p*
Sex (M:F)	72:15	23:0	129:40	.02[a]	.24	.03[a]	<.01[b]
Age, Years, Mean ± SD	18.27 ± 3.03	18.89 ± 3.06	18.77 ± 2.19	.15	—	—	—
IQ, Mean ± SD	96.20 ± 15.33	104.57 ± 13.63	109.98 ± 12.42	<.01[b]	<.01[b]	.02[a]	.10

Group differences on sex were tested via chi-square test; group differences on age and IQ were tested with regression models. Group differences in sex, age, and IQ were previously reported in another paper on this sample (14).

ADHD-P, attention-deficit/hyperactivity disorder persisters; ADHD-R, attention-deficit/hyperactivity disorder remitters; Ctrl, control group; F, female, M, male.

[a]$p < .05$.

[b]$p < .01$.

ADHD Diagnosis

The Diagnostic Interview for ADHD in adults (DIVA) (34) was conducted by trained researchers with parents of the ADHD probands to assess DSM-IV-defined ADHD presence and persistence. Raw scores for inattention and hyperactivity/impulsivity symptoms (range 0–9 for each dimension) were generated for each participant. Evidence of impairment commonly associated with ADHD was assessed with the Barkley's Functional Impairment Scale (33) during interviews with parents. Each item ranges from 0 (never or rarely) to 3 (very often). Participants were classified as "affected" at follow-up if they scored ≥6 in either the inattention or hyperactivity/impulsivity domains on the DIVA and ≥2 on two or more areas of impairments on the Barkley's Functional Impairment Scale. We defined ADHD outcome using a categorical definition of persistence based on diagnoses, as well as a dimensional approach based on levels of symptoms of ADHD and impairments measured as continuous traits.

IQ Assessment

An estimate of IQ was derived with the vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (35).

Task

The task was an adaptation of the Eriksen Flanker paradigm designed to increase cognitive load as used in previous studies (24,25,36). In each trial, a central black fixation mark was replaced by a target arrow (a black 18-mm equilateral triangle). Participants had to indicate whether this arrow pointed toward the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appeared 22 mm above and below the center of the target arrow 100 ms prior to each target arrow. Both flankers pointed in either the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 ms, with a new trial being presented every 1650 ms. Two hundred congruent and 200 incongruent trials were arranged in 10 blocks of 40 trials over 13 minutes. For further details on the task, see the Supplement. Cognitive-performance measures of mean reaction time (MRT), RTV (SD of reaction times), and number of errors (left-right errors occurring when participants chose the wrong left or right response) were calculated separately for congruent and incongruent conditions.

Electrophysiological Recording and Processing

The EEG was recorded from a 62-channel DC-coupled recording system (extended 10–20 montage), using a 500-Hz sampling rate, impedances under 10 kΩ, and the FCz electrode as the recording reference. The electro-oculograms were recorded from electrodes above and below the left eye and at the outer canthi. EEG data were analyzed using Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany). Raw EEG recordings were down-sampled to 256 Hz, rereferenced to the average of all electrodes (turning FCz into an active channel), and filtered using Butterworth band-pass filters (0.1–30 Hz, 24 dB/octave). All trials were visually inspected for electrical artifacts or obvious movement, and sections of data containing artifacts were removed manually. Ocular artifacts were identified using the InfoMax independent component analysis algorithm (37). Sections of data containing artifacts exceeding ±100 μV or with a voltage step >50 μV were automatically rejected. Baseline correction was applied using the −300 to −100 ms pretarget (−200 to 0 ms preflanker) interval.

Analyses of ERPs of performance monitoring were restricted to incongruent trials, as the task used in this study is known to elicit strong N2, ERN, and Pe components in high-conflict, but not in low-conflict, conditions (24,25,36). Data were segmented based on 1) stimulus-locked incongruent trials where a correct response was made and 2) response-locked (error-related) incongruent trials where an incorrect response was made. Individual averages were created based on each condition, requiring ≥20 clean segments for each participant. After averaging, the electrodes and latency windows for ERP analyses were selected based on previous studies (23–25,38), topographic maps, and the grand averages (Figures 1 and 2). The N2 was measured as maximum negative peak at the Fz and FCz electrodes between 250 and 450 ms after target onset. The ERN was defined with respect to the preceding positivity (PNe, −100 to 50 ms) and measured at FCz between 0 and 150 ms. This peak-to-peak measure has proven to be a robust measure of this component (20,23,39) and was favored over a peak-to-baseline (maximal amplitude) measure as the former distinguished ADHD from control participants in independent samples using this version of the Eriksen Flanker task (24,25,40); it was therefore the ideal

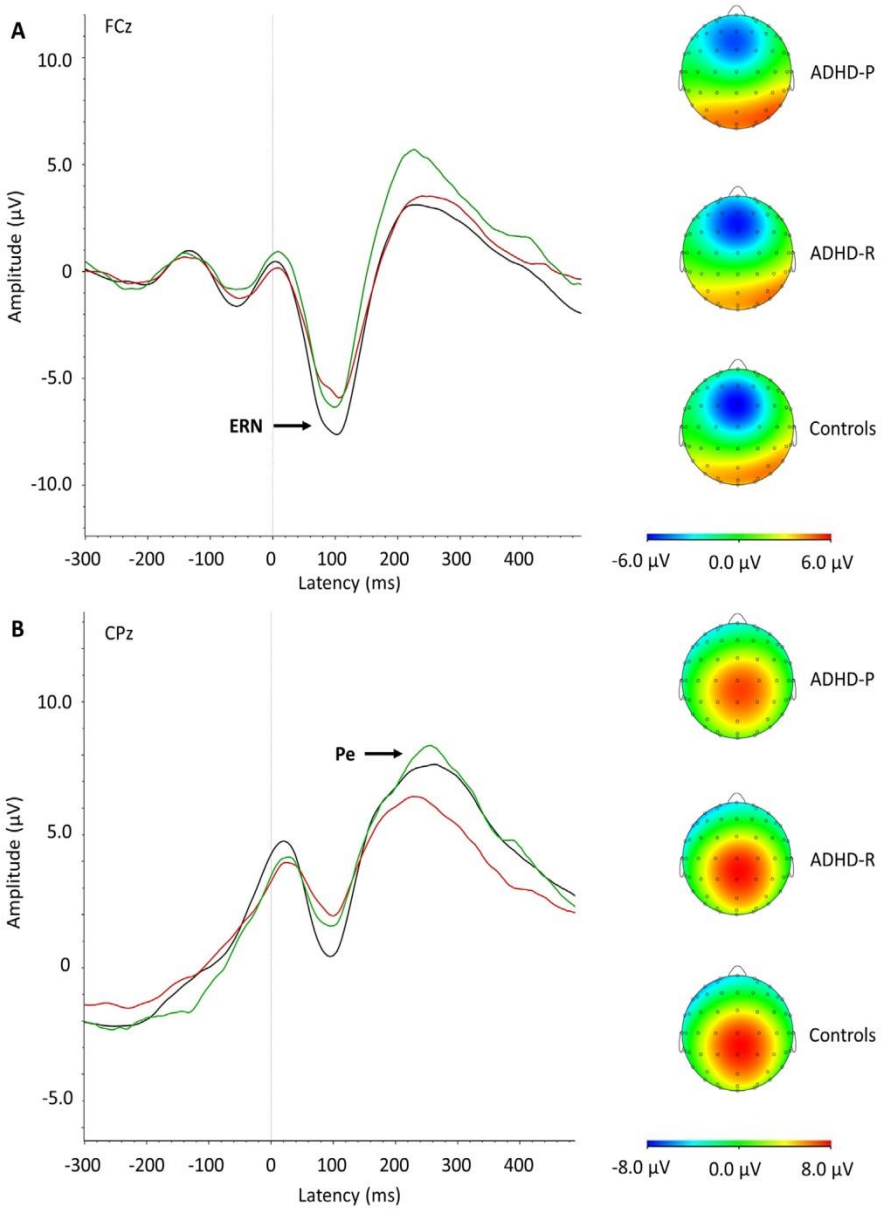

Figure 1. Grand average response-locked event-related potentials of the error-related negativity (ERN) at the FCz electrode between 0 and 150 ms **(A)** and the error-related positivity (Pe) at the CPz electrode between 150 and 450 ms **(B)** after an erroneous response on the incongruent trials for attention-deficit/hyperactivity disorder (ADHD) persisters (ADHD-P, in red), ADHD remitters (ADHD-R, in green), and control participants (Controls, in black), with topographic maps.

candidate in relation to ADHD remission/persistence (for further details see the Supplement). The Pe was measured as maximum positive peak at the CPz electrode between 150 and 450 ms after an erroneous response on incongruent trials.

Statistical Analyses

For RTV and errors, we tested overall effects of group (ADHD persisters, remitters, control participants), condition (congruent, incongruent), and group by condition interaction using random intercept models in Stata (StataCorp, College Station, TX) to control for genetic relatedness of the sibling pairs in a repeated-measures design. A random intercept model was also run to test the effect of group, scalp site (Fz, FCz) and group by site interaction on the N2. ERN and Pe were analyzed with regression models with dummy variables to identify overall group effects, controlling for sibling relatedness with the "robust cluster" command in Stata. Age correlated significantly with several of the cognitive-ERP measures (Supplemental Table S1) and was therefore included as a covariate in group analyses. On measures that indicated a group effect, post hoc regressions were performed. The majority of our sample consisted of male participants (80%), and thus primary analyses were performed on the whole sample without accounting for sex differences. As groups were not matched on sex (no female in the sample remitted

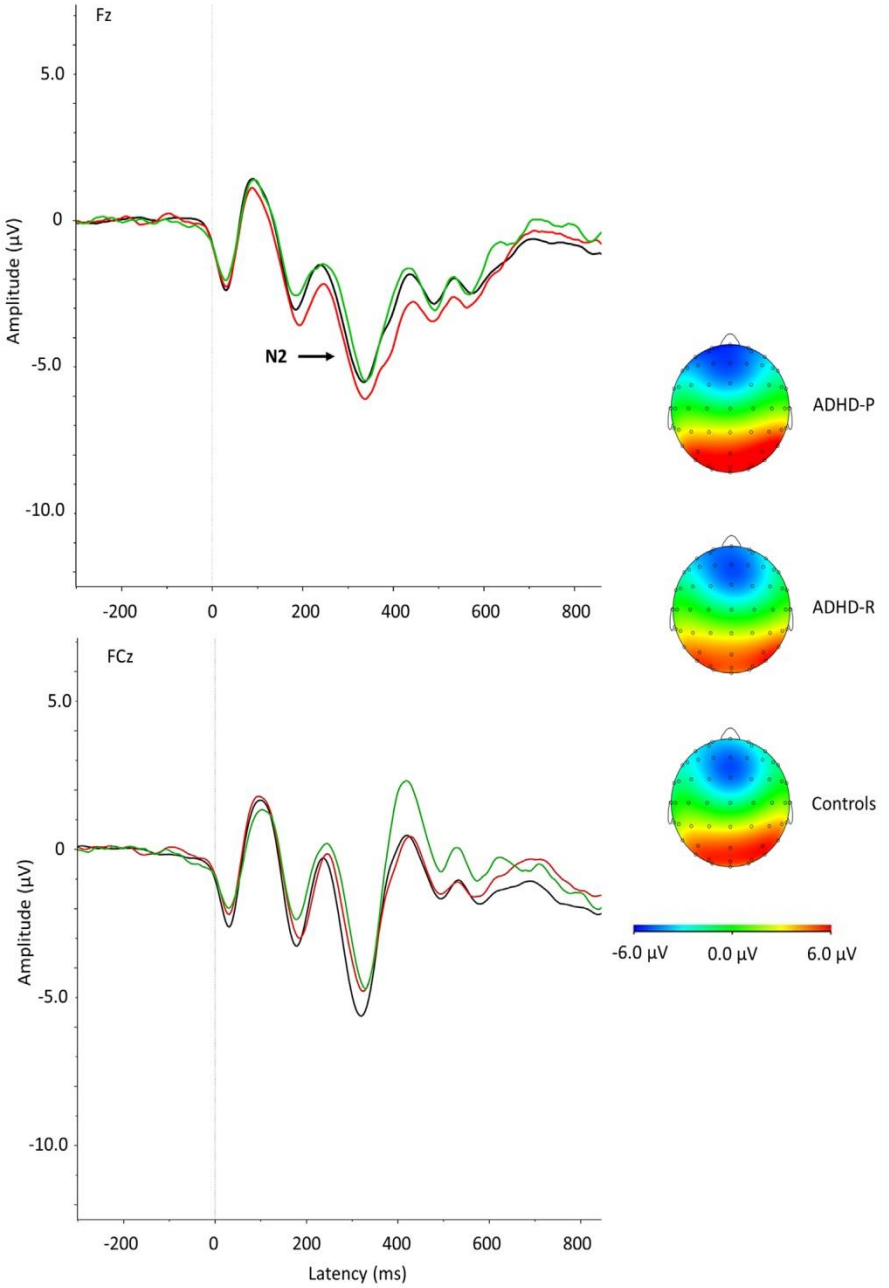

Figure 2. Grand average stimulus-locked event-related potentials of the N2 at the Fz and FCz electrodes between 250 and 450 ms after incongruent stimuli where a correct response was made for attention-deficit/hyperactivity disorder (ADHD) persisters (ADHD-P, in red), ADHD remitters (ADHD-R, in green), and control participants (Controls, in black), with topographic maps.

from ADHD) (Table 1), analyses were rerun with the female participants (15 ADHD persisters and 41 control participants) removed. Cohen's *d* effect sizes are presented along with means, SDs, and test statistics for the group analyses (Table 2), where 0.20 is considered a small effect, 0.50 a medium effect, and 0.80 a large effect (41). Pearson correlations examined which measures correlated with DIVA ADHD symptom scores and functional impairment in those with a childhood ADHD diagnosis, with age and sex included as covariates.

Because ADHD persisters had lower IQs than remitters did (Table 1) (14), and higher IQ in childhood was associated with ADHD remission at follow-up in this sample (31), all analyses were also rerun controlling for IQ. All cognitive-ERP measures were skewed and log-transformed to normal. Three participants (ADHD persisters) were excluded from the N2 analysis and 39 (13 ADHD persisters [15%], 3 ADHD remitters [13%], 23 control participants [14%]) from the ERN/Pe analysis due to having <20 artifact-free ERP segments, which is similar to previous studies using this paradigm

Table 2. Descriptive Statistics and Group Comparison on Cognitive-Performance and ERP Measures

				Group Comparison							Covarying IQ					
	ADHD-P	ADHD-R	Ctrl		ADHD-P vs. Ctrl		ADHD-P vs. ADHD-R		ADHD-R vs. Ctrl			ADHD-P vs. Ctrl		ADHD-P vs. ADHD-R		ADHD-R vs. Ctrl	
	Mean ± SD	Mean ± SD	Mean ± SD	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*p*	*d*	*p*	*d*	*p*	*d*	*p*
Performance																	
Congruent errors	10.89 ± 17.26	4.00 ± 3.85	4.14 ± 8.31	<.01[a]	.83[b]	<.01[a]	.75[c]	<.01[a]	.04	.95	<.01[a]	.55[c]	<.01[a]	.60[c]	.01[a]	.09	.89
Incongruent errors	57.87 ± 20.08	56.22 ± 20.75	48.87 ± 18.02	<.01[a]	.53[c]	<.01[a]	.06	.86	.46	.06[d]	<.01[a]	.32	.01[a]	.06	.98	.37	.11
Congruent MRT (ms)	355.82 ± 60.39	339.58± 38.99	336.25 ± 33.28	<.01[a]	.41	<.01[a]	.28	.23	.11	.63	.28	—	—	—	—	—	—
Incongruent MRT (ms)	449.87 ± 56.16	441.94 ± 33.44	431.68 ± 40.75	<.01[a]	.40	<.01[a]	.07	.73	.35	.07[d]	.44	—	—	—	—	—	—
Congruent RTV (ms)	114.26 ± 65.70	83.19 ± 28.22	76.24 ± 21.67	<.01[a]	1.00[b]	<.01[a]	.61[c]	<.01[a]	.35	.11	<.01[a]	.60[c]	<.01[a]	.42	.04[e]	.14	.25
Incongruent RTV (ms)	119.31 ± 80.64	88.18 ± 32.91	76.12 ± 22.84	<.01[a]	.97[b]	<.01[a]	.47	.04[e]	.50[c]	.02[e]	<.01[a]	.55[c]	<.01[a]	.24	.18	.30	.08[d]
ERPs																	
N2 at Fz (μV)	−7.23 ± 3.69	−6.91 ± 3.61	−6.57 ± 3.27	.02[e]	.30	.03[e]	.02	.91	.29	.19	.03	.25	.02[e]	.01	.88	.26	.20
N2 at FCz (μV)	−5.8 ± 3.74	−6.26 ± 3.57	−6.92 ± 3.81	.07[d]	.26	.08[d]	.18	.53	.08	.82	.11	—	—	—	—	—	—
ERN at FCz (μV)	7.78 ± 3.37	9.64 ± 4.11	10.08 ± 4.51	<.01[a]	.55[c]	<.01[a]	.52[c]	.05[e]	.06	.86	<.01[a]	.37	<.01[a]	.39	.09[d]	.01	.98
Pe at CPz (μV)	9.36 ± 4.23	10.96 ± 4.06	11.31 ± 4.27	<.01[a]	.44	<.01[a]	.44	.05[e]	.02	.88	.03[e]	.32	.03[e]	.36	.06[d]	.06	.79

Data on performance measures were available for the full sample (87 ADHD-P, 23 ADHD-R, and 169 control participants); data on the N2 were available for 84 ADHD-P, 23 ADHD-R, and 169 control participants; data on the PNe, ERN, and Pe were available for 74 ADHD-P, 20 ADHD-R, and 146 control participants. Overall effects of group, condition (on cognitive-performance measures), and site (on the N2) and interaction effects were tested with mixed models and reported in Supplemental Table S2. Only group effects were tested on the ERN and Pe, thus regression models (rather than mixed models) were used. Age was also included as a covariate in all analyses and its effects are not presented here for simplicity, but are available upon request.

ADHD-P, attention-deficit/hyperactivity disorder persisters; ADHD-R, attention-deficit/hyperactivity disorder remitters; Congruent, congruent condition; Ctrl, control; *d*, Cohen's *d* effect size; ERN, error-related negativity; ERP, event-related potential; Incongruent, incongruent condition; MRT, mean reaction time of correct response to targets; *p*, regression model significant testing; Pe, error-related positivity; RTV, reaction time variability to targets (i.e., SD of reaction time).

[a] $p \leq .01$.

[b] $d > .80$, indicating a large effect size.

[c] $d > .50$, indicating a medium effect size.

[d] $p \leq .09$.

[e] $p \leq .05$.

(24,25), and reflecting a similar exclusion ratio across groups.

RESULTS

Group Differences

An overall group effect emerged on all cognitive-performance and ERP measures (Table 2, Figures 1 and 2). Post hoc analyses showed that ADHD persisters had significantly higher MRT, RTV, number of errors, enhanced N2 (at Fz, but with a trend for reduction at FCz, pointing to topographic differences, as shown in Supplemental Figure S1) and reduced ERN and Pe compared with control participants, with small-to-large effect sizes. Significant differences between ADHD remitters and persisters emerged on congruent and incongruent RTV, congruent errors, ERN, and Pe with medium-to-large effect sizes. ADHD remitters did not differ from persisters on MRT in either condition, on incongruent errors and N2, with null-to-small effect sizes. ADHD remitters and control participants significantly differed on incongruent RTV, with a medium effect size, and at trend level with small effect sizes for incongruent errors and incongruent MRT.

Controlling for IQ, group effects on MRT in both conditions and N2 at FCz were nonsignificant (Table 2). Differences between remitters and persisters became nonsignificant in incongruent RTV and trends in ERN and Pe. Remitters and control participants differed at trend level in incongruent RTV, but not in incongruent errors. Results for other variables remained unchanged. When repeating the analyses with female participants removed, the difference between ADHD persisters ($n = 63$) and remitters ($n = 20$) became a trend for the ERN and nonsignificant for the Pe. Given the small female sample sizes ($n = 15$; of which only $n = 11$ had data on ERN and Pe) and the discrepancy in the size of male and female groups, sex differences were not directly tested. However, the effect sizes in the male-only sample ($d = 0.47$ for the ERN, $d = 0.34$ for the Pe) were comparable or only slightly reduced compared with those of the full sample. Remitters significantly differed from control participants on incongruent MRT,

Table 3. Pearson Correlations (Two-Tailed) of Cognitive Performance and ERP Measures With Interview-Based DIVA ADHD Symptoms and Clinical Impairment Within the ADHD Group Only (n = 110)

	Controlling for Age and Sex		Controlling for IQ, Age, and Sex	
	ADHD Symptoms	Impairment	ADHD Symptoms	Impairment
Congruent Errors	.15	.21[a]	.10	.17[b]
Incongruent Errors	.07	.03	.05	<.01
Congruent MRT (ms)	−.11	<.01	.07	−.09
Incongruent MRT (ms)	.05	−.07	−.01	.14
Congruent RTV (ms)	.21[a]	.13	.15	.12
Incongruent RTV (ms)	.21[a]	.18[b]	.14	.10
N2 at Fz (μV)	.04	.18[b]	.04	.18[b]
N2 at FCz (μV)	.07	.12	.10	.15
ERN at FCz (μV)	−.01	−.15	.03	−.11
Pe at CPz (μV)	−.20[a]	−.20[a]	−.20[a]	−.20[a]

ADHD, attention-deficit/hyperactivity disorder; Congruent, congruent condition; DIVA, Diagnostic Interview for ADHD in adults; ERN, error-related negativity; ERP, event-related potential; Incongruent, incongruent condition; MRT, mean reaction time of correct response to targets; Pe, error-related positivity; RTV, reaction time variability to targets (i.e., SD of reaction time).

[a] $p \leq .05$.

[b] $p \leq .09$.

congruent RTV, and incongruent RTV, but not on incongruent errors. All other results remained unchanged. For further details, see the Supplement.

Associations With ADHD Symptoms and Impairments

Among those with childhood ADHD (n = 110), both ADHD symptoms and impairment at follow-up significantly correlated with the Pe (Table 3). ADHD symptoms also significantly correlated with RTV in both conditions, and functional impairment correlated with congruent errors and at trend level with incongruent RTV and N2 at Fz. When IQ was controlled for, the correlation of ADHD symptoms or impairment with RTV became nonsignificant, and the correlation between functional impairment and congruent errors became a trend (Table 3).

DISCUSSION

In this first large-scale investigation of cognitive and neurophysiological performance monitoring in adolescents and young adults with ADHD, we found that ADHD remitters had enhanced cognitive processes of attention-vigilance (RTV and congruent errors) and neurophysiological error processing (ERN and Pe) compared with persisters. Attention-vigilance measures and conscious error processing were also associated with the continuum of ADHD symptoms and impairment at follow-up. Conversely, measures of executive control (incongruent errors), speed of processing (MRT), and neurophysiological conflict monitoring (N2) did not distinguish remitters from persisters, and thus they were not sensitive to remission or persistence of the disorder. Processes of attention-vigilance and neurophysiological error processing can be markers of remission from ADHD and may be sensitive to the effects of training or compensatory mechanisms.

RTV, measuring intraindividual variability in reaction time, and number of congruent errors in the low-conflict condition distinguished ADHD remitters from persisters, but not from control participants, and were also correlated with continuous ratings of ADHD symptoms and impairment. Impairments in such measures in the congruent condition of the flanker task may result from lapses in attention and index attention-vigilance processes. Neurophysiological measures of error processing (ERN and Pe) showed the same association with ADHD remission. Conscious error processing (Pe) also correlated with the continuous ADHD symptoms and functional impairments at follow-up. Of note, the group differences observed on this peak-to-peak ERN were likely explained by the voltage change from the PNe to the negative ERN peak (see the Supplement). This measure captures the response-locked oscillatory pattern immediately before and after an error is made and as such may reflect early attentional processes linked to automatic error detection. Conversely, incongruent errors in the high-conflict condition, likely reflecting a failure in executive control, and MRT in left-right responses at every trial, likely measuring speed of processing in this task that induces high cognitive demands, did not distinguish ADHD remitters from persisters. Similarly, neurophysiological conflict monitoring (N2) did not differ between ADHD groups, potentially indicating suboptimal parallel stimulus processing regardless of remission or persistence (17,42). Remitters also showed lower RTV in the incongruent condition compared with persisters but were still impaired when compared with control participants. Given the higher levels of executive control elicited in the incongruent condition, this could result from joint influences of both attention-vigilance and executive processes. Therefore, RTV in the incongruent condition may be less sensitive to remission than it is in the congruent condition.

Primary analyses did not control for IQ, as lower-mean IQ in ADHD samples represents one of multiple cognitive processes underlying ADHD pathophysiology (43,44), and the etiological influences shared between ADHD and IQ are largely separate from those shared with other cognitive impairments (45–47). Thus, by removing IQ effects when investigating the relationship between ADHD and cognitive-ERP variables, one may also control for features of ADHD related to IQ (48,49). In this sample, ADHD remission was associated with higher IQ measured both in childhood and at follow-up (14,31). As such, it may be that higher IQ represents a potential compensatory mechanism. To test the association between cognitive-ERP measures and remission or persistence beyond the influence of IQ, we also repeated the analyses covarying for IQ. When controlling for IQ, overall group differences for MRT were no longer significant, suggesting that group differences on this measure may reflect ADHD impairments related to IQ.

Moreover, remitters were more similar to persisters in some markers of remission (RTV, ERN, and Pe) when removing the IQ effects. This further points to an association between IQ and better cognitive-neurophysiological profiles in ADHD remitters.

The present study extends the findings in our previous investigation that used a cued continuous performance test (CPT-OX), a four-choice reaction time task, and Wechsler Abbreviated Scale of Intelligence measures of IQ and digit span (14). Attention-vigilance and error detection showed a similar pattern to that found in our previous analyses for preparation-vigilance measures (RTV, omission errors, ERP activity of response preparation, and delta and theta activity), whereas executive control (measured by incongruent errors), speed of processing (MRT for left-right responses), and conflict monitoring (N2) did not distinguish remitters from persisters, which is similar to measures of inhibition and working memory in our previous investigation (14). ADHD remitters showed an intermediate pattern between persisters and control participants on this latter group of measures: they showed no significant differences from either group on the N2, but there were trend-level differences from control participants on incongruent errors and MRT, suggesting that the latter two measures may potentially represent markers of enduring deficits. Our findings align with four recent studies reporting no differences between ADHD remitters and persisters in executive control (11–14), but not with two earlier studies that suggested a link from ADHD remission to better executive function (1,10). More broadly, our findings are in line with evidence for a separation of ADHD neurocognitive impairments into bottom-up and top-down processes supported by genetically sensitive studies (32,50). Our results are also consistent with reports of ADHD-sensitive improvement following rewards in RTV and ERPs of error processing (30,51,52), suggesting that such processes are malleable and may improve with the additional allocation of cognitive arousal and motivational incentives in ADHD samples. Future studies may further characterize the relationship between ADHD outcome and performance monitoring processes by using tasks with different ratios of congruent and incongruent trials, which may produce stronger enhancement of conflict processes (53), potentially coupled with single-trial measures to examine trial-to-trial adjustments (54).

A limitation of this study is that, despite the large sample size, the low ADHD remission rate at follow-up resulted in a relatively small group of remitters. Therefore, we could not rule out the possibility that some nonsignificant differences between remitters and other groups could be due to low power. However, we observed medium-to-large effect sizes (d = 0.44–0.75) between persisters and remitters in measures representing markers of remission, but small or negligible effect sizes (d = 0.02–0.28) in measures not sensitive to ADHD outcome at follow-up, suggesting this study had sufficient power to detect the major correlates of remission with the current sample sizes. Furthermore, when we repeated the analyses for male participants only, differences between remitters and persisters in the ERN and Pe were reduced. However, the small sample of female participants did not allow a direct examination of sex differences. Future studies that include a higher number of female participants are needed to further investigate these processes also in females. Finally, our sample included young adults as well as adolescents, who are still undergoing rapid cortical maturation. Although we controlled for age in all analyses, future follow-up assessments with participants having reached adulthood and when more ADHD participants may have remitted could clarify matters further.

Overall, we report that attention-vigilance and neurophysiological error processes were impaired in ADHD persisters but not in remitters and may be sensitive to compensatory mechanisms in those who remit from the disorder. These processes may be targets for nonpharmacological interventions or behavioral training aimed at alleviating some of the long-term outcomes of ADHD. Conversely, cognitive measures of executive control, speed of processing, and conflict monitoring were not sensitive to ADHD remission/persistence. Considering the importance of using a broad range of cognitive and neural measures in investigating the mechanisms underlying neurodevelopmental disorders (2), our cognitive and neurophysiological investigation provides an improved understanding of the trajectories to ADHD remission and persistence. Future studies should aim to investigate the neural sources and neurobiological mechanisms underlying these markers of remission in order to pave the way toward the development of new interventions aimed at stimulating processes that are sensitive to remission to reduce severe long-term outcomes of the disorder.

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CHAPTER 3 - Atypical functional connectivity in adolescents and adults with persistent and remitted ADHD

3.1 Abstract

Background: We previously provided initial evidence for cognitive and event-related potential markers of persistence/remission of attention-deficit/hyperactivity disorder (ADHD) from childhood to adolescence and adulthood. In this follow-up study, using a novel brain-network connectivity approach, we aimed to examine whether functional connectivity reflects a marker of ADHD remission, or an enduring deficit unrelated to ADHD outcome. **Methods:** High-density EEG was recorded in 110 adolescents and young adults with childhood ADHD (87 persisters, 23 remitters) and 169 typically-developing individuals during an arrow-flanker task, eliciting cognitive control. Functional connectivity was quantified with network-based graph theory metrics before target onset (pre-stimulus), during target processing (post-stimulus) and in the degree of change between pre-stimulus/post-stimulus. ADHD outcome was examined with parent-reported symptoms and impairment using both a categorical (DSM-IV) and a dimensional approach. **Results:** Graph-theory measures converged in indicating that, compared to controls, ADHD persisters showed increased connectivity in pre-stimulus theta, alpha and beta and in post-stimulus beta (all $p<.01$), and reduced pre-stimulus/post-stimulus change in theta connectivity ($p<.01$). In the majority of indices showing ADHD persister-control differences, ADHD remitters differed from controls (all $p<.05$), but not from persisters. Similarly, connectivity measures were not associated with continuous outcome measures of ADHD symptoms and impairment in participants with childhood ADHD. **Conclusions:** Adolescents and young adults with persistent and remitted ADHD share atypical over-connectivity profiles and reduced ability to modulate connectivity patterns with task demands, compared to controls. Brain connectivity impairments may represent enduring deficits in individuals with childhood ADHD irrespective of diagnostic status in adolescence/young adulthood.

3.2 Introduction

A coherent communication between different brain regions, or brain functional connectivity, is thought to have a key role in cognition and behaviour (Deco and Kringelbach, 2016, Bullmore and Sporns, 2009, Coben et al., 2017). Accumulating evidence suggests that atypical connectivity may be implicated in neurodevelopmental disorders (Castellanos and Aoki, 2016, Kitzbichler et al., 2015, Xing et al., 2017), such as attention-deficit/hyperactivity disorder (ADHD). Most studies to date have investigated brain connectivity in ADHD using functional magnetic-resonance imaging (fMRI), with reduced connectivity within and between brain regions/sub-networks during resting (e.g., within the default-mode network (DMN) and between DMN and executive networks) observed in individuals with ADHD (Fair et al., 2010, Sripada et al., 2014, Sun et al., 2012, Castellanos et al., 2008, Uddin et al., 2008). Evidence of increased resting-state connectivity within and between these regions, however, has also been reported in ADHD (Barbera et al., 2015, Hoekzema et al., 2014, McCarthy et al., 2013, Tian et al., 2006, Sidlauskaite et al., 2016, Castellanos and Aoki, 2016). Examining brain connectivity during task performance further allows a more direct characterisation of connectivity alterations underlying the impairments in cognition and behaviour associated with ADHD (Ernst et al., 2015, Finn et al., 2017). Task-based fMRI studies of ADHD show hypo-connectivity in fronto-striato-cerebellar networks during sustained attention (Rubia et al., 2009) and inhibition (van Rooij et al., 2015a, Cubillo et al., 2010, Vloet et al., 2010), and hyper-connectivity within the DMN (van Rooij et al., 2015a) and between networks of reward/cognitive control integration (Ma et al., 2016). Using the sub-second temporal resolution of electroencephalography (EEG), previous studies have further shown hypo- and hyper-connectivity in slower and faster brain oscillations from different cortical regions during rest (Clarke et al., 2007, Dupuy et al., 2008, Barry et al., 2005) and cognitive performance in individuals with ADHD (Murias et al., 2007, Mazaheri et al., 2014, Silberstein et al., 2016). Available task-based studies in children and adolescents with ADHD indicate reduced fronto-parietal theta-alpha connectivity (Mazaheri et al., 2010, Mazaheri et al., 2014), but also increased connectivity in alpha (Murias et al., 2007) and beta (Silberstein et al., 2016). No study to date has examined task-based EEG connectivity in adults with ADHD. Overall, despite inconsistencies regarding which brain networks may be hypo- and hyper-connected, available evidence points to atypical brain connectivity in ADHD.

While atypical functional connectivity has been documented both in children (Fair et al., 2010, Sripada et al., 2014, Sun et al., 2012) and adults (Mattfeld et al., 2014, Uddin et al., 2008, Castellanos et al., 2008) with ADHD, little is known on how these alterations map onto ADHD

developmental outcomes. ADHD persists, in full or in partial remission, in the majority of adolescents and adults clinically diagnosed in childhood (Faraone et al., 2006, Sibley et al., 2016). Yet, the evidence that some individuals remit across development may suggest the presence of (1) neural processes that are markers of remission, improving concurrently with clinical profiles and distinguishing individuals with persistent and remitted ADHD (ADHD "persisters" and "remitters", respectively); and of (2) enduring deficits that are unrelated to the clinical outcome, remaining impaired in both remitters and persisters (Halperin and Schulz, 2006). The identification of such measures may help elucidate the mechanisms underlying remission/persistence, and point to candidate biomarkers for the development of new interventions for ADHD. Most studies to date, using cognitive-performance indices, found that executive functioning measures do not distinguish between ADHD persisters and remitters, and are thus insensitive to ADHD outcomes (Pazvantoglu et al., 2012, Biederman et al., 2009, McAuley et al., 2014, Cheung et al., 2016, Michelini et al., 2016a). Fewer studies have investigated the neural underpinnings of remission/persistence. In a recent follow-up of adolescents and young adults with childhood ADHD, we found that cognitive and event-related potential (ERP) markers of executive control (inhibition, working memory, conflict monitoring) were insensitive to ADHD outcome (Cheung et al., 2016, Michelini et al., 2016a, James et al., 2017). Instead, cognitive, ERP and EEG power measures of preparation-vigilance and error detection were markers of remission, distinguishing ADHD remitters from persisters.

Considering the important role of brain connectivity in behaviour and cognition (Deco and Kringelbach, 2016, Bullmore and Sporns, 2009, Coben et al., 2017), the investigation of this brain-wide neural mechanism may provide new insight into the neural pathways of persistence and remission of ADHD. Only three studies to date have investigated functional connectivity in remitted and persistent ADHD, using fMRI (Clerkin et al., 2013, Mattfeld et al., 2014, Francx et al., 2015a). Two of these studies, using small samples, suggest that ADHD persisters may show lower functional connectivity than remitters and controls between the DMN and executive network during rest (Mattfeld et al., 2014) and between the thalamus and frontal areas during response preparation (Clerkin et al., 2013). Resting-state medial-dorsolateral functional associations in the prefrontal cortex, implicated in cognitive control, may instead be unrelated to ADHD outcome, and reduced in both ADHD remitters and persisters, compared to controls (Mattfeld et al., 2014). A larger-scale study, however, found higher connectivity in ADHD remitters than controls, with persisters showing intermediate profiles between remitters and controls (Francx et al., 2015a). Investigating brain connectivity using the excellent temporal resolution of EEG may provide further information in relation to ADHD remission/persistence by

capturing fast and transient changes in functional connectivity (not captured by fMRI) during cognitive processes (Coben et al., 2014, McLoughlin et al., 2014a). Yet, most EEG connectivity studies in ADHD to date present methodological limitations, such as the use of connectivity metrics contaminated by volume-conduction artefacts (i.e., the spreading and mixing of multiple brain sources at the scalp), which may produce inflated connectivity estimates (Nolte et al., 2004, Nunez et al., 1997). Recently developed network approaches, such as graph theory, may be further applied to characterise brain connectivity between large-scale brain networks and identify connectivity alteration (Bullmore and Sporns, 2009, Rubinov and Sporns, 2010, Castellanos and Aoki, 2016). Initial graph-theoretic evidence from two task-based studies shows atypical functional connectivity in children with ADHD (Xia et al., 2014, Liu et al., 2015). No study to date has examined measures of EEG connectivity in relation to longitudinal ADHD outcome.

In the present EEG study, we aimed to investigate brain functional connectivity during a cognitive control task in a follow-up of adolescents and adults with and without childhood ADHD. In previous analyses on these data we have shown that attention-vigilance cognitive processes and ERPs of error detection were markers of remission, while cognitive-ERP measures of executive and conflict processes were insensitive to ADHD outcome (Michelini et al., 2016a). Here, we aimed to test whether functional connectivity patterns, measured with graph-theory and connectivity metrics not contaminated by volume conduction, represent markers of ADHD remission or enduring deficits. We hypothesised that both ADHD remitters and persisters would display functional connectivity alterations during this task evoking high levels of cognitive control, consistent with most studies examining cognitive and EEG markers of executive processes (Pazvantoglu et al., 2012, Biederman et al., 2009, McAuley et al., 2014, Cheung et al., 2016, Michelini et al., 2016a).

3.3 Methods

3.3.1 Sample

The sample consisted of 279 participants who were followed up on average 5.8 years (SD=1.1) after assessments in childhood (Kuntsi et al., 2010), including 110 adolescents and young adults who met DSM-IV criteria for combined-type ADHD in childhood (10 sibling pairs and 90 singletons) and 169 control participants (76 sibling pairs and 17 singletons) (Cheung et al., 2016). Participants with ADHD were initially recruited from specialised ADHD clinics, and controls from

schools in the UK (Kuntsi et al., 2010). Exclusion criteria at both assessments were: IQ<70, autism, epilepsy, brain disorders, and any genetic/medical disorder associated with externalising behaviours that might mimic ADHD. Among those with childhood ADHD, at follow-up 87 (79%) continued to meet clinical (DSM-IV) levels of ADHD symptoms and impairment (ADHD persisters), while 23 (21%) were below the clinical cut-off (ADHD remitters) (Cheung et al., 2015). Among ADHD remitters, 14 displayed ≥5 symptoms of inattention or hyperactivity-impulsivity, but did not show functional impairment. Participants attended a single research session for clinical, IQ and cognitive-EEG assessments. An estimate of IQ was derived with the vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). ADHD persisters, remitters and controls did not differ in age, but there were significantly more males in the remitted group than in the other two groups, with no females among ADHD remitters (Table 3.1) (Cheung et al., 2016, Michelini et al., 2016a). ADHD persisters showed lower IQ compared to remitters and controls (Cheung et al., 2015, Cheung et al., 2016). 47% of participants with childhood ADHD were on drug treatment at follow-up, but the proportion of participants on medication did not differ between ADHD persisters and remitters (χ^2=1.95, p=0.16) (Cheung et al., 2016). A 48-hour ADHD medication-free period was required before assessments. Parents of all participants gave informed consent following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

3.3.2 ADHD diagnosis

The Diagnostic Interview for ADHD in Adults (DIVA) (Ramos-Quiroga et al., 2016) was conducted by trained researchers with parents of the ADHD probands, to assess DSM-IV-defined ADHD presence and persistence of the 18 ADHD symptoms. Evidence of impairment commonly associated with ADHD was assessed with the Barkley's functional impairment scale (BFIS) (Barkley and Murphy, 2006). Parent-report DIVA and impairments were used to determine ADHD status, as these were validated against objective markers (cognitive-performance and EEG measures) in this sample, whereas the same objective markers showed limited agreement with self-reported ADHD (Du Rietz et al., 2016). Participants were classified as "affected" at follow-up if they showed at least 6 items in either the inattention or hyperactivity-impulsivity domains on the DIVA, and two or more areas of impairments on the BFIS. We defined ADHD outcome using a categorical definition of persistence based on diagnoses, as well as a dimensional approach based on continuous levels of symptoms of ADHD and impairments.

Table 3.1. Sample demographics divided by group, with tests for differences between ADHD persisters, remitters and controls

	ADHD-R (n=23)	ADHD-P (n=87)	Ctrl (n=169)	Group Comparison			
					Ctrl vs ADHD-P	Ctrl vs ADHD-R	ADHD-P vs ADHD-R
	M:F	**M:F**	**M:F**	**p**	**p**	**p**	**p**
Gender	23:0	72:15	129:40	.02*	.24	<.01**	.03*
	mean (SD)	**mean (SD)**	**mean (SD)**	**p**	**p**	**p**	**p**
Age	18.89 (3.06)	18.27 (3.03)	18.77 (2.19)	.15	-	-	-
IQ	104.57 (13.63)	96.20 (15.33)	109.98 (12.42)	<.01**	<.01**	.10	.02*

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Ctrl = Control group; F = number of females; M = number of males.

*Notes: Group differences on gender were tested via Chi-square test; group differences on age and IQ were tested with linear regressions. Group differences in gender, age and IQ were previously reported in other papers on this sample (Cheung et al., 2016, Michelini et al., 2016a). **p<.01; *p<.05.*

3.3.3 Task

The task was an adaptation of the Eriksen Flanker paradigm designed to increase cognitive load (Albrecht et al., 2008, McLoughlin et al., 2014b). In each trial a central black fixation mark was replaced by a target arrow (a black 18 mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appeared 22 mm above and below the centre of the target arrow 100 ms before each target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, cognitive control and conflict monitoring are maximal during incongruent trials. When the target appeared, both target and flankers remained on the screen for 150 ms, with a new trial being presented every 1650 ms. Two-hundred congruent and 200 incongruent trials were arranged in 10 blocks of 40 trials. Only incongruent trials, known to elicit greater ADHD-control differences (McLoughlin et al., 2014b, Michelini et al., 2016a), were considered in the present analysis. For further details on the task, see Appendix B.

3.3.4 EEG recording and processing

The EEG was recorded from a 62-channel extended 10–20 system montage (Brain Products, GmbH, Munich, Germany), using a 500 Hz sampling-rate, impedances under 10 kΩ, and recording reference at FCz. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes (turning FCz into an active channel), and filtered using Butterworth band-pass filters (0.10-30 Hz, 24 dB/oct). All trials were visually inspected and sections of data containing electrical or movement artefacts were removed manually. Ocular artefacts were identified using Independent Component Analysis (ICA) (Jung et al., 2000). Sections of data containing artefacts exceeding ±100 μV or with a voltage step greater than 50 μV were automatically rejected. The artefact-free data were segmented in epochs between -650–1000 ms stimulus-locked to incongruent stimuli. Both trials with correct and incorrect responses were examined (Michelini et al., 2016a). Only data containing ≥20 clean segments for condition were included in analyses, leaving 271 participants (83 ADHD persisters, 22 remitters, 166 controls) for correctly-responded trials and 240 (75 ADHD persisters, 20 remitters, 145 controls) for incorrectly-responded trials.

3.3.5 Connectivity analysis

3.3.5.1 Calculation of functional connectivity and graph-theory metrics

We examined functional brain connectivity with the imaginary part of coherence (iCoh), a functional association index able to detect interactions between EEG signals occurring with a certain time delay, thus ignoring instantaneous interaction between neighbouring electrodes likely produced by volume conduction (Hinkley et al., 2010, Nolte et al., 2004, Palva and Palva, 2012) (for further explanation see Appendix B). Values of iCoh for all possible electrode pairs (62x62) were computed in the theta (4-8 Hz), alpha (8-12 Hz) and beta (12-20 Hz) bands (Figure 3.1), which have previously been implicated in cognitive processes engaging top-down control networks requiring coherent activity between brain areas (Buzsaki and Draguhn, 2004, Uhlhaas and Singer, 2006, Wang, 2010), such as the fronto-parietal network (Klimesch et al., 2010, Klimesch et al., 2007, Halgren et al., 2002, Capotosto et al., 2009).

The high multi-dimensionality of the iCoh measures was disentangled with a graph-theory approach. Unthresholded weighted iCoh matrices were used, in line with previous studies (Xing et al., 2017, Hardmeier et al., 2014, Boersma et al., 2013, van den Heuvel et al., 2010), where each connection is equivalent to the measured iCoh of two electrodes. Graph theory metrics measure the degree of network segregation (i.e., the tendency of brain regions to form local clusters with dense functional interconnections), and network integration and efficiency (i.e., the capacity of the network to become interconnected and efficiently exchange information between brain regions) (Bullmore and Sporns, 2009, Sporns, 2014). The following commonly-used graph measures were calculated (Ahmadlou et al., 2012, Boersma et al., 2013, Liu et al., 2015, Xing et al., 2017, Fraga Gonzalez et al., 2016): average clustering coefficient (the probability of neighbouring nodes of being inter-connected, reflecting local connectedness); global efficiency (how efficient the network is in transferring information); characteristic path length and diameter (respectively, the average number of edges along the shortest paths, and the largest possible distance, between all possible pairs of nodes). Values of iCoh and graph-theory metrics were computed with the BioNeCT toolbox (https://sites.google.com/site/bionectweb/home; Coben et al., 2017) and Matlab custom scripts separately for correctly- and incorrectly-responded trials in stimulus-locked windows, before target (pre-stimulus; -500–0 ms) and during target processing (post-stimulus; 0–500 ms).

3.3.6 Statistical analyses

3.3.6.1 Categorical analysis based on diagnostic status

Connectivity metrics were examined with random intercept linear models (i.e., multilevel regression models) in Stata 14 (StataCorp, College Station, TX), testing for effects of group (ADHD persisters vs remitters vs controls), time window (pre-stimulus vs post-stimulus), response (correct vs incorrect) and their interaction (group-by-window-by-response). When the three-way interaction was not statistically significant, only statistically significant main effects and two-way interactions were included. For all measures, the within-group degree of change from pre-stimulus to post-stimulus was compared across groups using difference scores. All models controlled for age and took into account the degree of clustering due to family status. Cohen's d effect sizes are presented along with test statistics, where d≥0.20 is a small effect, d≥0.50 a medium effect and d≥0.80 a large effect (Cohen, 1988). Given the large number of hypotheses tested, sensitivity analyses applied multiple-testing corrections with false discovery rate (FDR) on post-hoc tests with the "multproc" package (Simes, 1986).

Since 80% of our sample consisted of males, but groups were not fully matched on sex (Table 3.1), analyses were performed on the whole sample and then repeated with females (15 ADHD persisters, 41 controls) removed. As in this sample ADHD persisters had a lower IQ than remitters (Cheung et al., 2016), and childhood IQ predicted ADHD outcome at follow-up (Cheung et al., 2015), all analyses were also re-run controlling for IQ to examine whether IQ contributes to the results. Finally, to examine brain connectivity within and between cortical regions, analyses were repeated using iCoh values within and between clusters of electrodes in different scalp regions (anterior/central/posterior) and between the two hemispheres (left/right) (for further details, see Appendix B).

3.3.6.2 Dimensional analysis with ADHD symptoms/impairment

The association between connectivity and the continua of ADHD symptoms and impairment within individuals with childhood ADHD were examined with random intercept linear models using DIVA ADHD symptom and impairment scores as independent variables, controlling for age and sex and clustering for family status. All analyses were re-run, firstly, correcting for multiple testing, and, secondly, controlling for IQ.

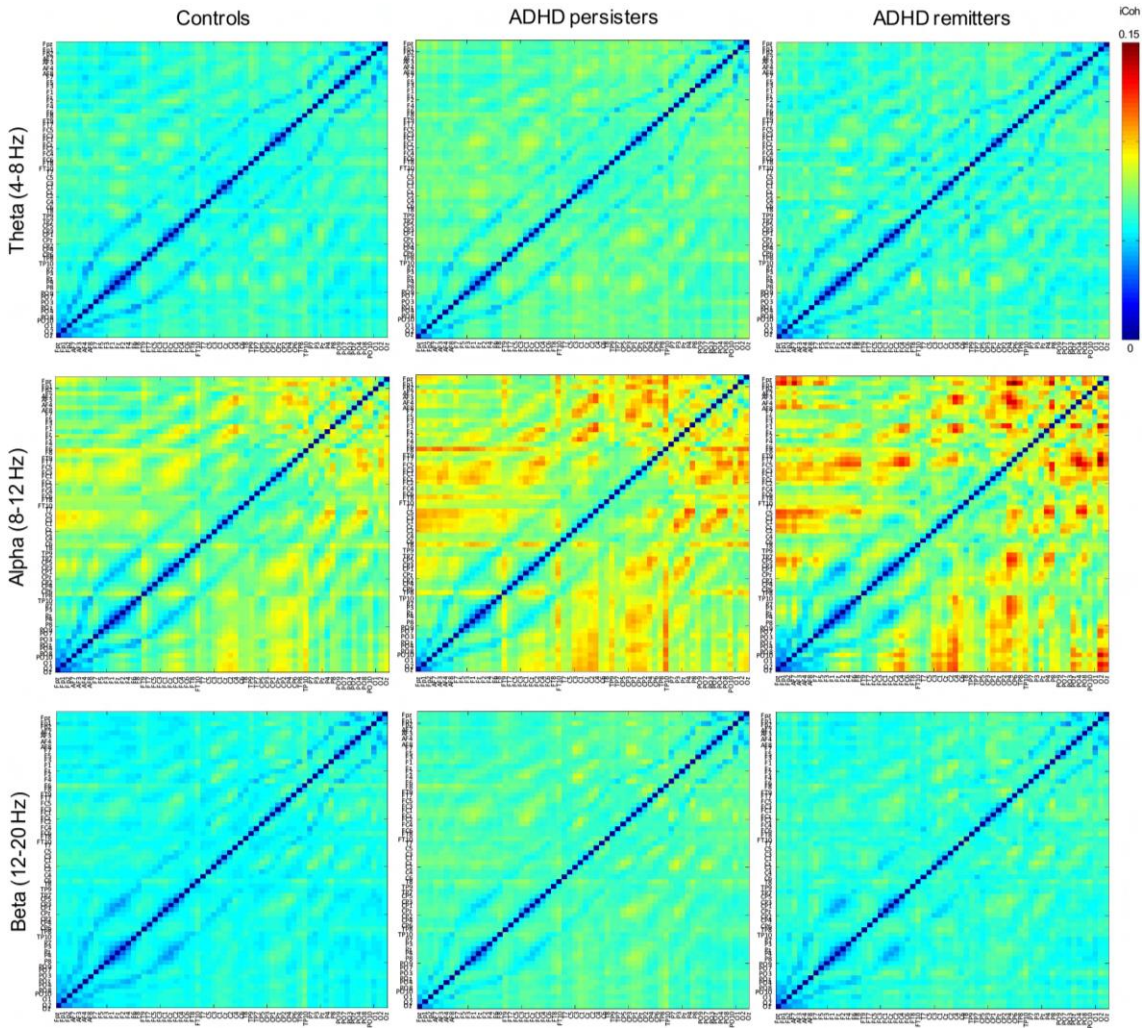

***Figure 3.1**. Connectivity matrices showing values of imaginary part of coherence (iCoh) in the theta, alpha and beta band for correctly-responded trials by group (ADHD persisters, remitters and controls).*

3.4 Results

3.4.1 Differences between ADHD persisters, remitters and controls

Post-hoc analyses revealed that, in correctly-responded trials, ADHD persisters showed greater clustering coefficient, global efficiency and mean iCoh, and lower path length and diameter compared to controls at all frequency bands in the pre-stimulus window, and only in beta in the post-stimulus windows (Table 3.2, Figure 3.2). ADHD remitters showed lower pre-stimulus diameter in theta and beta, lower pre-stimulus path length in alpha and beta, and lower post-stimulus diameter in beta, compared to controls. ADHD remitters did not differ from persisters in any connectivity measure in correctly-responded trials, except diameter in beta (where remitters were intermediate between controls and persisters, and significantly differed from both groups) (Table 3.2). These findings indicate increased functional connectivity in both ADHD persisters and remitters compared to controls during correct trials. In error trials, group differences only emerged for clustering coefficient, global efficiency and mean iCoh in post-stimulus theta: both ADHD persisters and remitters showed reduced values in these measures (indicating lower connectivity) compared to controls, but did not differ from each other (Table 3.2). All three groups showed increased connectivity (greater clustering coefficient, global efficiency and mean iCoh; decreased path length and diameter) in incorrect compared to correct trials, in both pre-stimulus and post-stimulus windows (Table S3.1-S3.2, Appendix B). All main and interaction effects are shown in Table S3.2, Appendix B.

Among measures showing significant group-by-window interactions (all in theta, all except diameter in alpha, none in beta; Table S3.2, Appendix B), significant within-group differences in changing from pre-stimulus to post-stimulus windows emerged in all groups for all theta connectivity measures, in controls only for clustering coefficient, path length and mean iCoh in the alpha band, and in both ADHD groups for global efficiency in alpha (Table 3.3). ADHD persisters and remitters exhibited a significantly lower degree of change than controls in all measures of theta connectivity, but no differences emerged between the two ADHD groups (Table 3.3).

Multiple-testing corrections (controlling the FDR at 15%) on post-hoc group comparisons (separately for ADHD persisters vs controls, ADHD remitters vs controls, ADHD persisters vs remitters) showed that all significant group differences that were statistically significant remained significant, except for the difference between ADHD persisters and remitters in beta

diameter. All significant group differences on measures of pre-stimulus/post-stimulus change remained statistically significant.

All results remained unchanged when rerunning analyses on the male-only sample (Table S3.3-S3.4, Appendix B), except that the p-values of certain tests that were statistically significant in the full sample became trend-level effects (p=0.05-0.10) (see Appendix B). All effect sizes were similar to those on the full sample, suggesting that these non-significant results may be due to lower power in this smaller sample.

Results of group comparisons on connectivity measures in pre- and post-stimulus were largely unchanged when IQ was included as a covariate in categorical analyses (Table S3.5, Appendix B), while few differences between persisters and controls on measures of pre-stimulus/post-stimulus change in theta and alpha connectivity during error trials were no longer significant (Table S3.6, Appendix B).

Results of analyses on group differences in local connectivity within cortical regions (within anterior/central/posterior regions and within left/right hemispheres) and these three cortical regions and two hemispheres, were consistent with those on whole-brain connectivity (see Appendix B).

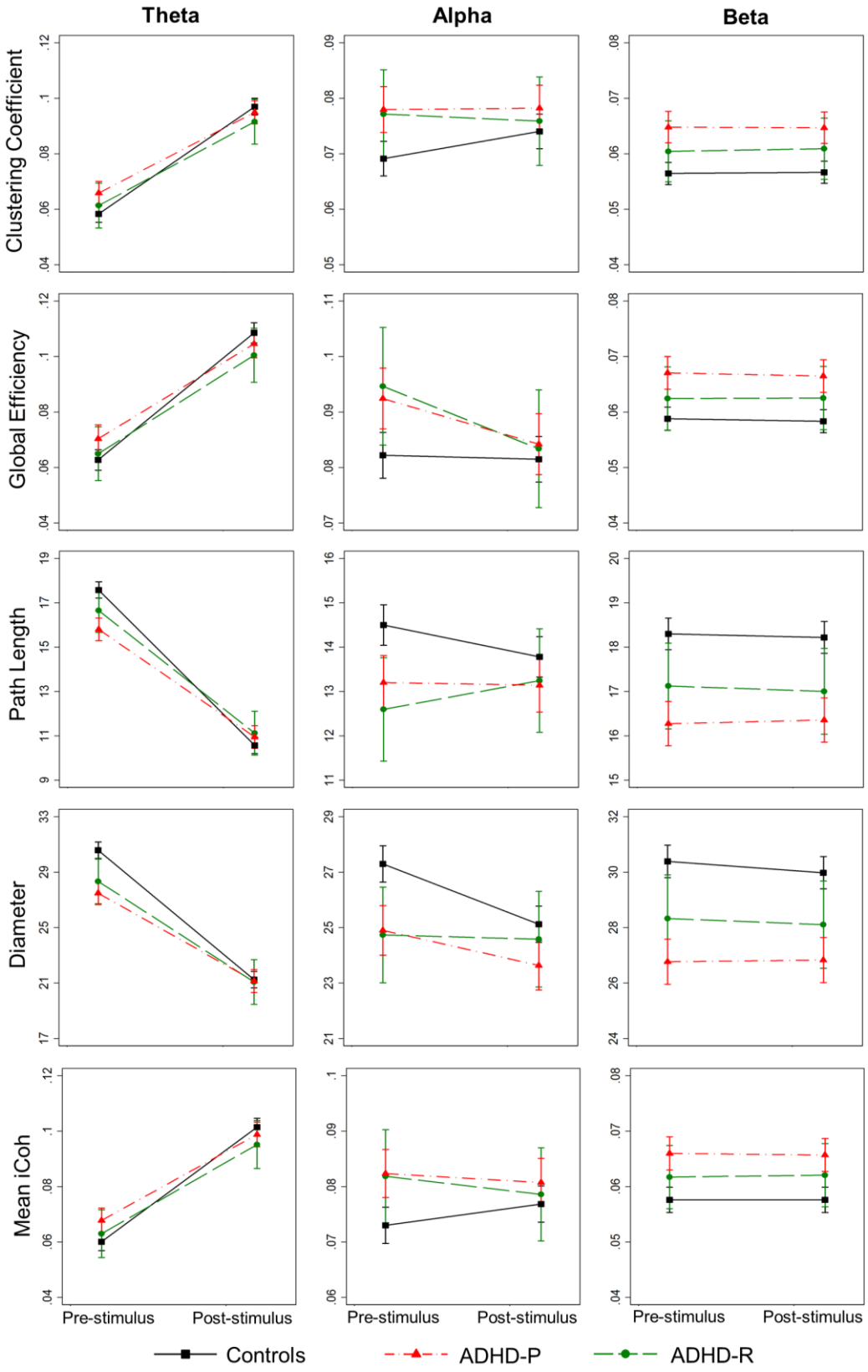

Figure 3.2. *Results of the categorical analyses comparing ADHD persisters, remitters and controls on measures of graph theory and imaginary part of the coherence (iCoh) in the theta, alpha and beta band for correctly-responded trials.*

Table 3.2. Group comparisons on graph-theory and imaginary coherence measures

			Group comparison					
		Overall Group	**Ctrl vs ADHD-P**		**Ctrl vs ADHD-R**		**ADHD-R vs ADHD-P**	
THETA		**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Pre, Corr*	0.016*	0.004**	*0.63*	0.880	0.29	0.139	0.35
	Pre, Err	0.544	-	-	-	-	-	-
	Post, Corr	0.401	-	-	-	-	-	-
	Post, Err	<0.001***	<0.001***	0.35	0.017*	0.30	0.955	0.05
Global efficiency	*Pre, Corr*	0.053	0.019*	*0.51*	0.901	0.16	0.145	0.37
	Pre, Err	0.568	-	-	-	-	-	-
	Post, Corr	0.189	-	-	-	-	-	-
	Post, Err	<0.001***	<0.001***	0.35	0.019*	0.30	0.916	0.05
Path length	*Pre, Corr*	0.012*	<0.001***	*0.58*	0.095	0.30	0.130	0.30
	Pre, Err	0.434	-	-	-	-	-	-
	Post, Corr	0.338	-	-	-	-	-	-
	Post, Err	0.122	-	-	-	-	-	-
Diameter	*Pre, Corr*	<0.001***	<0.001***	*0.64*	0.012*	0.49	0.352	0.17
	Pre, Err	0.646	-	-	-	-	-	-
	Post, Corr	0.976	-	-	-	-	-	-
	Post, Err	0.279	-	-	-	-	-	-
Mean imaginary coherence	*Pre, Corr*	0.024*	0.007**	*0.60*	0.952	-0.25	0.140	0.35
	Pre, Err	0.562	-	-	-	-	-	-
	Post, Corr	0.319	-	-	-	-	-	-
	Post, Err	<0.001***	<0.001***	0.35	0.019*	0.30	0.955	0.06
ALPHA		**Overall Group**	**Ctrl vs ADHD-P**		**Ctrl vs ADHD-R**		**ADHD-R vs ADHD-P**	

		p	p	d	p	d	p	d
Average clustering coefficient	*Pre, Corr*	0.001**	<0.001***	0.44	0.097	0.42	0.636	0.06
	Pre, Err	0.415	-	-	-	-	-	-
	Post, Corr	0.328	-	-	-	-	-	-
	Post, Err	0.084	-	-	-	-	-	-
Global efficiency	*Pre, Corr*	0.003**	0.002**	0.32	0.054	0.39	0.976	0.04
	Pre, Err	0.325	-	-	-	-	-	-
	Post, Corr	0.816	-	-	-	-	-	-
	Post, Err	0.152	-	-	-	-	-	-
Path length	*Pre, Corr*	<0.001***	<0.001***	0.32	0.005**	0.47	0.539	0.13
	Pre, Err	0.709	-	-	-	-	-	-
	Post, Corr	0.201	-	-	-	-	-	-
	Post, Err	0.235	-	-	-	-	-	-
Diameter	*Corr*	<0.001***	<0.001***	0.41	0.054	0.30	0.610	0.13
	Err	0.444	-	-	-	-	-	-
Mean imaginary coherence	*Pre, Corr*	0.001**	<0.001***	0.40	0.073	0.39	0.684	0.04
	Pre, Err	0.341	-	-	-	-	-	-
	Post, Corr	0.501	-	-	-	-	-	-
	Post, Err	0.064	-	-	-	-	-	-
BETA		**Overall Group**	**Ctrl vs ADHD-P**		**Ctrl vs ADHD-R**		**ADHD-R vs ADHD-P**	
		p	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	<0.001***	<0.001***	*0.79*	0.097	*0.51*	0.101	0.31
	Err	0.135	-	-	-	-	-	-
Global efficiency	*Corr*	<0.001***	<0.001***	*0.73*	0.137	0.44	0.098	0.31
	Err	0.154	-	-	-	-	-	-
Path length	*Corr*	<0.001***	<0.001***	*0.76*	0.004**	*0.52*	0.090	0.27

	Err	0.343	-	-	-	-	-	-
	Corr	<0.001***	<0.001***	**0.83**	0.003**	*0.53*	0.044*	0.31
Diameter	*Err*	0.221	-	-	-	-	-	-
Mean imaginary coherence	*Corr*	<0.001***	<0.001***	*0.77*	0.097	*0.49*	0.101	0.31
	Err	0.135	-	-	-	-	-	-

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = trials with correct responses; Ctrl = Control group; d = Cohen's d effect size; Err = trials with incorrect responses; p = random intercept linear model significance testing; Pre = pre-stimulus time window; Post = post-stimulus time window.
Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly-responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Full results are presented in Table S3.2, Appendix B. Since neither diameter in the alpha band, nor any measures in the beta band showed a significant group-by-window interaction, post-hoc effects of group were tested for with correctly- and incorrectly-responded trials collapsed across pre-stimulus and post-stimulus time windows. Post-hoc comparisons between groups were run only on measures showing a significant overall group effect. Age was also included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 83 ADHD persisters, 22 remitters, 166 controls; and in incorrectly-responded trials for 75 ADHD persisters, 20 remitters, 145 controls.
**p<0.05; **p<0.01; ***p<0.001. d≥0.20 = small effect size, d≥0.50 = medium effect (in italics) and d≥0.80 = large effect size (in bold).*

Table 3.3. Within- and between-group effects on measures of change between pre-stimulus and post-stimulus windows in graph-theory and imaginary coherence measures

		Within-Group Change			Between-Group Change					
		Ctrl	ADHD-P	ADHD-R	Ctrl vs ADHD-P		Ctrl vs ADHD-R		ADHD-R vs ADHD-P	
THETA		**p**	**p**	**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	<0.001***	<0.001***	<0.001***	0.001**	0.42	0.010*	0.41	0.981	0.05
	Err	<0.001***	<0.001***	<0.001***	0.011*	0.33	0.618	0.06	0.370	0.26
Global efficiency	*Corr*	<0.001***	<0.001***	<0.001***	0.002**	0.40	0.014*	0.38	0.997	0.04
	Err	<0.001***	<0.001***	<0.001***	0.017*	0.31	0.643	0.06	0.400	0.25
Path length	*Corr*	<0.001***	<0.001***	<0.001***	<0.001***	*0.61*	0.014*	0.44	0.506	0.19
	Err	<0.001***	<0.001***	<0.001***	0.058	0.27	0.776	0.11	0.209	0.36
Diameter	*Corr*	<0.001***	<0.001***	<0.001***	<0.001***	*0.61*	0.016*	0.43	0.499	0.19
	Err	<0.001***	<0.001***	<0.001***	0.058	0.20	0.776	0.14	0.209	0.33
Mean imaginary coherence	*Corr*	<0.001***	<0.001***	<0.001***	0.001**	0.42	0.011*	0.40	0.995	0.05
	Err	<0.001***	<0.001***	<0.001***	0.013*	0.33	0.632	0.06	0.378	0.26
		Ctrl	**ADHD-P**	**ADHD-R**	**Ctrl vs ADHD-P**		**Ctrl vs ADHD-R**		**ADHD-R vs ADHD-P**	
ALPHA		**p**	**p**	**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	0.002**	0.910	0.767	0.055	0.27	0.091	0.38	0.704	0.09
	Err	0.001**	0.981	0.599	0.069	0.28	0.267	0.16	0.468	0.13
Global efficiency	*Corr*	0.728	0.004**	0.045*	0.071	0.27	0.147	0.40	0.705	0.11
	Err	0.155	0.029*	0.683	0.019*	0.38	0.140	0.25	0.389	0.15
Path length	*Corr*	0.002**	0.856	0.319	0.124	0.20	0.049*	0.42	0.349	0.23
	Err	0.011*	0.831	0.931	0.023*	0.37	0.094	0.33	0.743	0.07
Mean imaginary coherence	*Corr*	0.020*	0.491	0.472	0.064	0.27	0.111	0.37	0.735	0.08
	Err	0.001**	0.545	0.791	0.015*	0.40	0.087	0.30	0.469	0.13

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = trials with correct responses; Ctrl = Control group; d = Cohen's d effect size; Err = trials with incorrect responses; p = random intercept linear model significance testing.

Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly-responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Full results are presented in Table S3.2, Appendix B. Post-hoc tests on within- and between-group effects of change were run only on measures showing a significant group-by-window interaction. Since this interaction was not significant in diameter in the alpha band or in any measures in the beta band, post-hoc within- and between-groups effects of change were not tested. Age was also included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 83 ADHD persisters, 22 remitters, 166 controls; and in incorrectly-responded trials for 75 ADHD persisters, 20 remitters, 145 controls.

**p<0.05; **p<0.01; ***p<0.001. d≥0.20 = small effect size, d≥0.50 = medium effect (in italics).*

3.4.2 Association with ADHD symptoms and impairment

In dimensional analyses on participants with childhood ADHD, no association emerged between ADHD symptoms and any of the measures of connectivity in theta, alpha or beta frequencies in correct or error trials (Table 3.4). Functional impairment was not associated with any connectivity measure in the theta band, but showed associations with a subgroup of measures in alpha and beta in correct and error trials (Table 3.4). Results remained largely unchanged when controlling for IQ (Table S3.7, Appendix B). Statistically significant associations were no longer significant when applying multiple-testing corrections.

Table 3.4. Dimensional associations between graph-theory and imaginary coherence measures and interview-based DIVA ADHD symptom counts and clinical impairment within the ADHD group only, controlling for age and gender

		ADHD symptoms		Impairment	
THETA		**β (95% CIs)**	**p**	**β (95% CIs)**	**p**
Average clustering coefficient	*Pre, Corr*	<0.001 (-0.001;0.001)	0.964	<0.001 (-0.001;0.001)	0.163
	Pre, Err	<0.001 (-0.001;0.001)	0.844	<0.001 (-0.000;0.001)	0.110
	Post, Corr	<0.001 (-0.001;0.001)	0.827	<0.001 (-0.001;0.001)	0.111
	Post, Err	-0.001 (-0.002;0.001)	0.315	<0.001 (-0.001;0.001)	0.494
Global efficiency	*Pre, Corr*	<0.001 (-0.001;0.001)	0.685	<0.001 (-0.001;0.001)	0.393
	Pre, Err	<0.001 (-0.001;0.001)	0.969	<0.001 (-0.000;0.001)	0.110
	Post, Corr	<0.001 (-0.001;0.001)	0.667	0.001 (-0.001;0.001)	0.194
	Post, Err	-0.001 (-0.002;0.001)	0.196	-0.001 (-0.001;0.001)	0.120
Path length	*Pre, Corr*	0.029 (-0.127;0.185)	0.716	-0.052 (-0.135;0.032)	0.226
	Pre, Err	-0.017 (-0.148;0.114)	0.797	-0.053 (-0.123;0.016)	0.132
	Post, Corr	0.041 (-0.086;0.169)	0.528	-0.030 (-0.098;0.039)	0.395
	Post, Err	0.053 (-0.045;0.151)	0.290	0.013 (-0.040;0.066)	0.630
Diameter	*Pre, Corr*	0.067 (-0.185;0.320)	0.601	-0.072 (-0.211;0.067)	0.310
	Pre, Err	-0.044 (-0.259;0.170)	0.685	-0.083 (-0.196;0.031)	0.153
	Post, Corr	0.032 (-0.171;0.236)	0.756	-0.059 (-0.167;0.049)	0.287
	Post, Err	0.084 (-0.84;0.251)	0.328	0.008 (-0.080;0.096)	0.861
Mean imaginary coherence	*Pre, Corr*	<0.001 (-0.001;0.001)	0.898	<0.001 (-0.001;0.001)	0.204
	Pre, Err	<0.001 (-0.001;0.001)	0.878	<0.001 (-0.000;0.001)	0.110
	Post, Corr	<0.001 (-0.001;0.001)	0.778	0.001 (-0.001;0.001)	0.134
	Post, Err	-0.001 (-0.002;0.001)	0.268	<0.001 (-0.001;0.000)	0.306
		ADHD symptoms		**Impairment**	
ALPHA		**β (95% CIs)**	**p**	**β (95% CIs)**	**p**
Average clustering coefficient	*Pre, Corr*	<0.001 (-0.001;0.001)	0.894	<0.001 (-0.001;0.001)	0.708
	Pre, Err	<0.001 (-0.001;0.002)	0.578	0.001 (-0.000;0.001)	0.135
	Post, Corr	<0.001 (-0.001;0.001)	0.500	<0.001 (-0.001;0.001)	0.012*
	Post, Err	0.001 (-0.001;0.001)	0.204	0.001 (0.000;0.001)	0.034*
Global efficiency	*Pre, Corr*	<0.001 (-0.002;0.002)	0.794	<0.001 (-0.001;0.001)	0.450
	Pre, Err	<0.001 (-0.001;0.002)	0.738	0.001 (-0.000;0.001)	0.245
	Post, Corr	<0.001 (-0.001;0.001)	0.563	<0.001 (0.000;0.001)	0.046*
	Post, Err	0.001 (-0.001;0.002)	0.216	0.001 (0.001;0.001)	0.031*
Path length	*Pre, Corr*	<0.001 (-0.205;0.205)	0.998	0.043 (-0.069;0.154)	0.452
	Pre, Err	-0.018 (-0.154;0.118)	0.793	-0.044 (-0.117;0.001)	0.229
	Post, Corr	-0.036 (-0.163;0.091)	0.580	-0.066 (-0.133;0.000)	0.050
	Post, Err	-0.062 (-0.152;0.027)	0.172	-0.050 (-0.099;-0.002)	0.042*
Diameter	*Pre, Corr*	-0.042 (-0.344;0.259)	0.784	-0.037 (-0.204;0.129)	0.659
	Pre, Err	-0.085 (-0.290;0.120)	0.417	-0.090 (-0.202;0.022)	0.114
	Post, Corr	-0.058 (-0.270;0.153)	0.588	-0.122 (-0.233;-0.012)	0.030*
	Post, Err	-0.110 (-0.273;0.053)	0.185	-0.079 (-0.168;0.010)	0.083

Mean imaginary coherence	*Pre, Corr*	<0.001 (-0.001;0.001)	0.973	<0.001 (-0.001;0.001)	0.981
	Pre, Err	<0.001 (-0.001;0.002)	0.631	0.001 (-0.000;0.001)	0.156
	Post, Corr	<0.001 (-0.001;0.001)	0.505	<0.001 (0.000;0.001)	0.016*
	Post, Err	0.001 (-0.001;0.001)	0.204	0.001 (0.000;0.001)	0.033*
BETA		**ADHD symptoms**		**Impairment**	
		β (95% CIs)	**p**	**β (95% CIs)**	**p**
Average clustering coefficient	*Pre, Corr*	<0.001 (-0.001;0.001)	0.278	<0.001 (-0.000;0.001)	0.014*
	Pre, Err	<0.001 (-0.001;0.001)	0.613	<0.001 (-0.001;0.001)	0.077
	Post, Corr	<0.001 (-0.001;0.001)	0.435	<0.001 (0.000;0.001)	0.049*
	Post, Err	<0.001 (-0.001;0.001)	0.666	<0.001 (-0.001;0.001)	0.153
Global efficiency	*Pre, Corr*	<0.001 (-0.001;0.001)	0.372	<0.001 (-0.001;0.001)	0.014*
	Pre, Err	<0.001 (-0.001;0.001)	0.650	<0.001 (-0.000;0.001)	0.069
	Post, Corr	<0.001 (-0.001;0.001)	0.572	<0.001 (-0.001;0.001)	0.065
	Post, Err	<0.001 (-0.001;0.001)	0.688	<0.001 (-0.000;0.001)	0.152
Path length	*Pre, Corr*	-0.071 (-0.114;0.081)	0.361	-0.086 (-0.166;-0.006)	0.035*
	Pre, Err	-0.038 (-0.152;0.075)	0.508	-0.054 (-0.115;0.006)	0.080
	Post, Corr	-0.052 (-0.201;0.097)	0.490	-0.066 (-0.146;0.015)	0.110
	Post, Err	-0.046 (-0.164;0.072)	0.444	-0.045 (-0.107;0.017)	0.153
Diameter	*Pre, Corr*	-0.144 (-0.390;0.102)	0.251	-0.148 (-0.277;0.019)	0.024*
	Pre, Err	-0.091 (-0.292;0.109)	0.372	-0.077 (-0.183;0.029)	0.157
	Post, Corr	-0.125 (-0.372;0.121)	0.320	-0.108 (-0.241;0.026)	0.114
	Post, Err	-0.085 (-0.286;0.117)	0.410	-0.057 (-0.163;0.049)	0.294
Mean imaginary coherence	*Pre, Corr*	<0.001 (-0.001;0.001)	0.301	<0.001 (-0.001;0.001)	0.013*
	Pre, Err	<0.001 (-0.001;0.001)	0.620	<0.001 (-0.000;0.001)	0.072
	Post, Corr	<0.001 (-0.001;0.001)	0.478	<0.001 (-0.000;0.001)	0.054
	Post, Err	<0.001 (-0.001;0.001)	0.676	<0.001 (-0.000;0.001)	0.153

Abbreviations: β = regression coefficient; CIs = confidence intervals; Corr = trials with correct responses; Err = trials with incorrect responses; p = random intercept linear model significance testing; Pre = pre-stimulus time window; Post = post-stimulus time window. Data in correctly-responded trials were available for 105 childhood ADHD participants (83 ADHD persisters, 22 remitters); and in incorrectly-responded trials for 95 childhood ADHD participants (75 ADHD persisters, 20 remitters).

Notes: Random intercept linear models tested for the effect of ADHD symptom count/impairment on each connectivity measure.

**p<0.05.*

3.5 Discussion

Using a network-based EEG functional connectivity approach, our results indicate that ADHD persisters show widespread over-connectivity underlying cognitive-control processes compared to controls, as well as reduced adjustments of connectivity with changed task demands. ADHD remitters showed similar impairments as persisters, and differed from controls in most measures of connectivity and connectivity adjustments. These findings indicate that hyper-connectivity and reduced ability to modulate connectivity patterns with task demands characterise adolescents and young adults with both persistent and remitted ADHD. Atypical functional connectivity during cognitive-control processes may thus represent an enduring deficit in adolescents and adults with childhood ADHD, irrespective of their current diagnostic status.

Two main connectivity impairments emerged in individuals with persistent ADHD compared to controls. Firstly, ADHD persisters showed increased global connectivity (higher iCoh), network segregation (higher clustering coefficient), efficiency (higher global efficiency) and integration (lower path length and diameter) at all frequency bands prior to target onset in trials with correct behavioural responses, as well as during target processing in beta oscillations. The increases in functional connectivity are consistent with a previous EEG study reporting pre-target over-connectivity in children with ADHD (Silberstein et al., 2016), and more generally supports evidence indicating hyper-connectivity in ADHD (van Rooij et al., 2015a, Ma et al., 2016, Murias et al., 2007, Mazaheri et al., 2014). Connectivity in theta, alpha and beta oscillations during cognitive tasks is associated with cognitive processes engaging control networks and requiring coordination of activity between distributed brain areas (Buzsaki and Draguhn, 2004, Uhlhaas and Singer, 2006, Wang, 2010). Here, over-connectivity in these frequency ranges in persistent ADHD may reflect exaggerated interactions between brain regions, both during the inactive pre-stimulus period and during cognitive target processing. Considering the high cognitive demands induced by incongruent stimuli in this highly effortful task, which requires a response at every trial, increased connectivity (especially in the beta band) may reflect hyper-connectivity in executive control networks. Secondly, while all groups showed increased theta connectivity in changing from pre-stimulus to post-stimulus windows, this change was reduced in ADHD persisters compared to controls. This result in individuals with ADHD may point to a reduced ability to modulate brain connectivity patterns in slow oscillations from a relatively inactive context to a condition requiring cognitive engagement. This finding is in line with previous reports indicating reduced regulation of brain activity in ADHD between different

cognitive states (Rommel et al., 2016, Skirrow et al., 2015, Cheung et al., 2017). Overall, these findings show widespread connectivity impairments underlying cognitive-control processes in ADHD persisters, and advance our understanding of the neural underpinnings of persistent ADHD in adolescence and early adulthood.

Our study represents the first investigation into EEG connectivity in adolescents and adults with remitted ADHD. In several connectivity measures sensitive to impairments in persisters, ADHD remitters were impaired compared to controls and indistinguishable from persisters, consistent with our hypotheses. ADHD remitters also showed the same reduction in all measures of pre-stimulus/post-stimulus change in theta connectivity displayed by persisters. As such, brain connectivity impairments were insensitive to ADHD outcome (remission/persistence) in adolescence and early adulthood, and may represent enduring deficits irrespective of current diagnostic status. Findings from dimensional analyses supported these results, as most connectivity measures were unrelated to continuous levels of ADHD symptoms and impairments in participants with childhood ADHD. Of note, while results of categorical analyses were largely unchanged after correcting for multiple testing, the few significant associations between connectivity and functional impairment did not survive multiple-testing corrections. Overall, these connectivity findings in remitters are consistent with previous cognitive-EEG studies, including our previous analyses on this sample (Cheung et al., 2016, Michelini et al., 2016a), reporting that executive-functioning measures were insensitive to ADHD outcomes in adolescence and adulthood (Pazvantoglu et al., 2012, Biederman et al., 2009, McAuley et al., 2014, Cheung et al., 2016, Michelini et al., 2016a). They also partially align with results from a previous resting-state connectivity fMRI study, which found over-connectivity in remitters compared to controls and no differences between remitters and persisters (Francx et al., 2015a). A clinical implication is that connectivity impairments in executive-control processes may not be suitable targets for interventions for ADHD, consistent with previous evidence of no effects of stimulants on EEG connectivity in ADHD (Clarke et al., 2005, Dupuy et al., 2008). Future EEG studies should examine whether connectivity during less effortful activities, such as rest or non-executive processes, represent markers of remission, similar to cognitive-EEG measures of non-executive processes in our previous studies (Cheung et al., 2016, James et al., 2017, Michelini et al., 2016a).

Of note, while widespread group differences emerged in correctly-responded trials, group differences in error trials, likely representing a failure of cognitive control, emerged only in three measures of post-stimulus theta connectivity. The limited group differences in incorrect

responses may suggest that a failure in brain connectivity may attenuate the differences in brain-network profiles of neurotypical individuals from individuals with ADHD, who are prone to making more incorrect responses (Michelini et al., 2016a). In addition, all groups showed greater connectivity before and during incorrect responses than correct responses. A suboptimal pattern of pre-stimulus and post-stimulus over-connectivity underlying cognitive control processes may thus lead to a dysfunctional behavioural response, both in neurotypical individuals and in individuals with childhood ADHD. Future family model-fitting analyses (James et al., 2016) will investigate the phenotypic and aetiological associations between brain connectivity and cognitive-performance impairments in ADHD, which will provide new insights into the inter-relationships between these impairments.

A limitation of this study is that, despite the large sample, the low ADHD remission rate at follow-up resulted in a relatively small group of remitters. Therefore, we could not exclude the possibility that some non-significant group differences could be due to low power. However, the moderate effect sizes (d=0.38-0.53) between ADHD remitters and controls, but negligible or small (d=0.02-0.36) between remitters and persisters, in measures showing ADHD persister-control differences suggest that we had sufficient power to detect, with the current sample sizes, differences in connectivity with at least moderate effect sizes. In addition, our sample included young adults as well as adolescents, who are still undergoing rapid cortical maturation. While analyses controlled for age, future follow-up assessments with participants having reached adulthood could provide further insight into developmental patterns. Finally, while the current EEG connectivity analyses allowed precise temporal resolution and connectivity estimates unaffected by volume-conduction artefacts, the relatively poor spatial resolution of scalp-EEG did not allow precise localisation of the brain networks. Yet, results of local connectivity within and between cortical regions were consistent with those of whole-brain analyses, indicating comparable effects in more localised networks.

In conclusion, we report new evidence of shared atypical connectivity profiles in adolescents and young adults with persistent and remitted ADHD. These connectivity alterations may represent enduring deficits and neural signatures associated with having a history of childhood ADHD, but unrelated to current diagnostic status. Connectivity impairments underlying executive processes may represent associated characteristics or risk factors in ADHD (Johnson, 2012), which do not follow the developmental pathways of clinical profiles. Future studies should explore the presence of potential compensatory mechanisms in individuals with remitted ADHD that enable developmental improvements in clinical profiles and non-executive cognitive

processes (Cheung et al., 2016, James et al., 2017, Michelini et al., 2016a), despite persistence of enduring connectivity alterations.

CHAPTER 4 - The aetiological structure of cognitive-neurophysiological impairments in ADHD in adolescence and young adulthood

4.1 Abstract

Background: Adolescents and adults with attention-deficit/hyperactivity disorder (ADHD) show multiple cognitive-neurophysiological impairments. Previous studies in children with ADHD have identified two partially-separable familial factors underlying cognitive dysfunction, but evidence in adolescents and adults is lacking. Here, we investigate the aetiological structure of cognitive-neurophysiological impairments in ADHD in adolescence and young adulthood. **Methods**: In a sample of 356 participants from ADHD and control sibling pairs (mean age: 18 years, range: 11-27 years), factor analyses and multivariate familial models were run on data on IQ, digit span forward (DSF), digit span backward (DSB), and cognitive-performance and event-related potential (ERP) measures from a cued continuous performance task, an arrow-flanker task and a four-choice reaction time task. **Results**: Three familial factors (cF_{1-3}) were identified, which captured the familial covariation of ADHD with nine cognitive-ERP measures. cF_1 loaded on IQ, mean reaction time (MRT) and reaction time variability (RTV); cF_2 on DSF and DSB; and cF_3 on number of errors and ERPs of inhibition and error processing. All three factors showed significant familial overlap with ADHD ($r_{cF1\text{-}ADHD}$=.50; $r_{cF2\text{-}ADHD}$=-.36; $r_{cF3\text{-}ADHD}$=-.66). Non-familial influences showed the same factor structure, except for IQ that clustered with digit span measures. Non-familial influences on MRT and RTV largely overlapped with those on ADHD, while other non-familial effects were largely measure-specific. **Conclusions**: Three partially separable familial factors substantially accounted for the phenotypic association between cognitive-neurophysiological measures and ADHD in adolescence and adulthood. These results identify multiple aetiological pathways leading to cognitive and brain dysfunction in adolescent and adult ADHD.

4.2 Introduction

The majority of children clinically diagnosed with ADHD continue to meet ADHD diagnostic criteria in full or in partial remission in adolescence and adulthood (Biederman et al., 2009, Cheung et al., 2015, van Lieshout et al., 2016b, Karam et al., 2015, Faraone et al., 2006). In addition to symptoms of inattention and hyperactivity-impulsivity, adolescents and adults with ADHD typically show the same wide range of impairments in multiple cognitive functions that also characterise children with this disorder (Cheung et al., 2016, Kuntsi et al., 2010, Uebel et al., 2010, Hervey et al., 2004). For example, deficits in executive processes, such as inhibition and working memory, and in non-executive processes, such as preparation-vigilance impairments, have been found in individuals with ADHD in adolescence and adulthood (Hervey et al., 2004, Mostert et al., 2015, Cheung et al., 2016). The investigation of brain activity during cognitive tasks has further revealed widespread neurophysiological impairments, such as atypical brain activity during error processing, attentional allocation and response inhibition, in adolescents and adults with ADHD (Michelini et al., 2016b, Cheung et al., 2016, McLoughlin et al., 2009, Woltering et al., 2013, Groom et al., 2010a). The evidence of multiple cognitive and brain abnormalities in ADHD has contributed to a shift in the theoretical understanding of the disorder: from models that propose the existence of a single deficit, for example in inhibition (Barkley, 1997), as responsible for the multiple cognitive impairments, to models that argue for multiple underlying factors and pathways to ADHD (Castellanos and Proal, 2012, Halperin and Schulz, 2006, Johnson, 2012).

Twin and family studies have consistently reported high genetic/familial influences and limited-to-no role of the shared environment on ADHD (Faraone et al., 2005, Burt et al., 2012). In childhood, the genetic/familial influences on ADHD also show strong overlap with those on cognitive impairments (Andreou et al., 2007, Frazier-Wood et al., 2012, Kuntsi et al., 2010, Wood et al., 2010, Wood et al., 2011). Sibling studies have revealed two partially separable familial factors underlying the structure of cognitive impairments in ADHD in children, one capturing reaction time variability (RTV) and another capturing executive function, such as response accuracy (Kuntsi et al., 2010) and working memory (Frazier-Wood et al., 2012). IQ may also represent a separate process, as the genetic/familial effects that ADHD shares with IQ are largely separate from those that ADHD shares with other cognitive impairments (Wood et al., 2010, Wood et al., 2011, Rommelse et al., 2008c). Although ADHD persists in a significant number of individuals diagnosed in childhood, the extent to which these cognitive impairments show a

similar aetiological structure and share familial influences with ADHD in adolescents and adults is still unknown.

In our recent follow-up study of adolescents and young adults with a childhood combined-type ADHD diagnosis, we found a separation between impairments in cognitive and brain function processes in relation to ADHD outcomes (persistence/remission) at follow-up. Cognitive and neurophysiological measures of preparation-vigilance processes (e.g., RTV, omission errors, ERPs of response preparation), error detection and IQ were uniquely linked to ADHD persistence/remission at follow-up (Cheung et al., 2016, Michelini et al., 2016a, James et al., 2017), as individuals with persistent ADHD, but not with remitted ADHD, showed impairments in these measures. IQ in childhood further predicted ADHD persistence/remission, suggesting that IQ may represent a moderator of outcome (Cheung et al., 2015). In contrast, executive function measures (e.g., working memory and inhibition), despite being sensitive to impairments in ADHD persisters, were unrelated to ADHD outcome, as individuals with persistent and remitted ADHD were indistinguishable on these measures (Cheung et al., 2016, Michelini et al., 2016a). Overall, we proposed that, in adolescents and young adults with ADHD, cognitive-neurophysiological impairments may reflect three processes: (1) markers of persistence/remission (e.g., preparation-vigilance measures), (2) processes that are not associated with ADHD outcome (executive function), and (3) potential moderators of ADHD outcome (IQ) (Cheung et al., 2016). All three processes were impaired in adolescents and adults with persistent ADHD, suggesting a possible phenotypic separation of impairments in these three cognitive-neurophysiological processes in persistent ADHD. Yet, it remains unclear whether one or multiple aetiological factors underlie the association between such impairments and the disorder, as no study to date has examined the aetiology of multiple cognitive and brain impairments in adolescent and adult ADHD.

The present study aims to investigate, for the first time, the aetiological structure underlying cognitive-neurophysiological processes in ADHD in adolescence and early adulthood, in our follow-up of individuals from ADHD and control sibling pairs initially assessed in childhood (Kuntsi et al., 2010, Andreou et al., 2007, Wood et al., 2011, Wood et al., 2009). In previous analyses at follow-up, we found a broad range of impairments in cognitive and brain functions in individuals with persistent ADHD compared to controls (Cheung et al., 2016, Michelini et al., 2016a, Cheung et al., 2017). Here, we aim to take the most comprehensive approach to date in examining whether one or multiple aetiological processes underlie such impairments with persistent ADHD in this age group. We predict that, in line with studies on cognitive impairments

in children (Frazier-Wood et al., 2012, Kuntsi et al., 2010, Wood et al., 2011), multiple and partially separable aetiological processes would account for the presence of impairments in cognitive and brain function in the disorder.

4.3 Methods

4.3.1 Sample

The sample consisted of 404 participants, including 226 participants from ADHD sibling pairs (each including one DSM-IV ADHD proband and one affected or unaffected sibling) and 178 participants from control sibling pairs (both without ADHD) who had taken part in our previous research (Kuntsi et al., 2010, Chen et al., 2008) (for further details on the sample, see Appendix C). At initial assessment (age range: 6-17 years), ADHD participants recruited from specialist clinics and their closest-age siblings were invited to participate. Control participants were recruited from schools. At follow-up, which took place on average 5.8 years after the childhood assessment, 30 childhood ADHD probands were excluded for no longer meeting DSM-IV ADHD criteria (n=25), not having combined-type ADHD in childhood (n=3), or due to EEG equipment failure (n=2). Nine siblings of ADHD probands were excluded as they were unaffected in childhood but met DSM-IV ADHD criteria at follow-up (n=3) or their diagnostic status could not be determined due to missing parent-reported data on impairment (n=6). Nine controls were excluded due to meeting ADHD criteria at follow-up based on parent-reported ADHD ratings (Barkley Informant Rating Scale; Barkley and Murphy, 2006). The final sample for analyses consisted of 87 individuals with persistent ADHD and 100 unaffected siblings (69 full pairs, 49 singletons), and 169 control siblings (76 full pairs, 17 singletons) (Table 4.1). Among participants with persistent ADHD, 60% (n=52) met criteria for the combined subtype, 32% (n=28) met criteria for predominantly inattentive subtype and 8% (n=7) met criteria for predominantly hyperactivity-impulsivity subtype at follow-up. Written informed consent was obtained from all participants and the study was approved by the London-Surrey Borders Research Ethics Committee (NRES 09/H0806/58).

Table 4.1. Sample demographic information divided by group, with test for statistical difference

	ADHD probands (n=87)	Unaffected siblings (n=100)	Controls (n=169)	p	ADHD probands vs Controls	ADHD probands vs Unaffected siblings	Unaffected siblings vs Controls
					p	p	p
Sex (M:F)	72:15	43:57	129:40	**<.001**	.21	**<.001**	**<.001**
Age	18.31 (3.03)	18.56 (3.33)	17.75 (2.17)	.08	.14	.53	**.03**

Abbreviations: ADHD, attention deficit hyperactivity disorder; F, female; M, male.
Notes: Significant (p<0.05) differences are indicated in bold. Group differences on sex were tested via Chi-square test; group differences on other measures were tested with linear regressions. Group differences between ADHD and control participants were reported in previous analyses on this sample (Cheung et al., 2016, Michelini et al., 2016a).

4.3.2 ADHD diagnosis

ADHD diagnostic status in ADHD sibling pairs was assessed with the Diagnostic Interview for ADHD in Adults (DIVA) (Ramos-Quiroga et al., 2016), a semi-structured interview designed to evaluate the DSM-IV criteria for childhood and adult ADHD. Evidence of impairment commonly associated with ADHD was assessed with the Barkley's functional impairment scale (BFIS) (Barkley and Murphy, 2006), by trained researchers, along with the DIVA during interviews with parents. A separate interview was conducted with the ADHD probands and their siblings. Parent-report DIVA and impairments were used to determine ADHD status, as these were validated against objective markers (cognitive-performance and EEG measures) in this sample, whereas the same objective markers showed limited agreement with self-reported ADHD (Du Rietz et al., 2016). ADHD symptoms were assessed in control participants using the parent-rated Barkley Informant Rating Scale (Barkley and Murphy, 2006).

4.3.3 Procedure

Participants attended a single 4-hour research session (including breaks) for IQ, digit span and cognitive–EEG assessments (Table 4.2). For each sibling pair in both ADHD and control groups, one of the siblings was administered the IQ and digit span assessment, followed by a battery of three cognitive-EEG tasks, and vice versa for the other sibling. This was counterbalanced by proband-sibling group. The three tasks in the cognitive-EEG battery were administered in the same order. For those prescribed stimulants (n=52), a 48-hour ADHD medication-free period was required prior to cognitive-EEG assessments.

4.3.4 Electrophysiological recording and analysis

The EEG was recorded from a 62 channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 kΩ, and FCz as the recording reference. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. EEG data were analysed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and filtered using Butterworth band-pass filters (0.1-30 Hz, 24 dB/oct). Electrical or movement artefacts were removed following visual inspection. Ocular artefacts were corrected using the infomax Independent Component Analysis (ICA) algorithm (Jung et al., 2000). Sections of data containing artefacts exceeding ±100 µV or with a voltage step >50 µV

were automatically rejected. ERPs were extracted from the CPT-OX (Cue-P3, CNV, NoGo-P3), arrow flanker task (N2, ERN, Pe in the incongruent condition) and Fast task (P3 in the baseline condition) following procedures used in previous analyses on this sample (Cheung et al., 2016, Michelini et al., 2016a, Cheung et al., 2017) (Appendix C).

Table 4.2. Short description of the tasks included in the cognitive assessment and cognitive-EEG battery

Task name	Description	Measures extracted from the task
Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999)	The vocabulary and block design subtests were used to derive an estimate of IQ.	Total IQ.
Digit span subtest from Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991), or the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997)	The digit span subtest from the WISC-III or the WAIS-III was administered to participants aged below 16 and aged 16 or above, respectively, to obtain digit span forward (DSF) and backward (DSB). The forward test measures short-term verbal memory, while the backward test is a measure of working memory.	DSF, DSB.
Cued Continuous Performance Test (CPT-OX) (Doehnert et al., 2008, Valko et al., 2009)	The CPT-OX task consists of 400 letter arrays formed of a centre letter with incompatible flankers on each side, and probes attention, preparation and response inhibition. Stimuli are presented for 150ms with a SOA (stimulus onset asynchrony) of 1.65s in a pseudorandomised order at the centre of a computer monitor. The task involves the presentation of 80 Cues (XOX) followed either by 40 Go (OXO) and 40 NoGo (XDX) stimuli, alternated with random letter arrays as distractors. Participants are instructed to respond only to Cue-Go sequences, and to withhold the response in presence of a NoGo stimulus, of a Go not preceded by a Cue (40 trials), or of any other irrelevant letters. Task duration was approximately 11 min.	*Cognitive performance*: mean reaction time (MRT), reaction time variability (RTV, i.e. SD of RTs), commission errors (CE, i.e. response to NoGo), omission errors (OE, i.e. non-response to Go). *ERPs*: Cue-P3 (attentional orienting), CNV (response preparation) and NoGo-P3 (response inhibition).
Eriksen Arrow Flanker Task (Albrecht et al., 2008, McLoughlin et al., 2009)	This performance monitoring task is an adaptation of the Eriksen Flanker paradigm designed to increase cognitive load for adults. In each trial, a central black fixation mark was replaced by a target arrow. Participants are instructed to indicate whether	*Cognitive performance*: MRT, RTV and number of errors (left-right errors occurring when participants

	this arrow points towards the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appear above and below the centre of the target arrow 100ms prior to each target arrow. Both flankers either point in the same (congruent) or opposite (incongruent) direction to the target. Conflict monitoring is maximal during the incongruent condition. When the target appears, both target and flankers remain on the screen for a further 150ms, with a new trial being presented every 1.65s. Trials were arranged in ten blocks of 40 trials. Task duration was approximately 13 min.	chose the wrong response); all obtained separately for congruent and incongruent conditions. *ERPs*: N2 (conflict monitoring), ERN (automatic error processing) and Pe (conscious error processing), all obtained from the incongruent condition only.
Fast task (Andreou et al., 2007)	This is a four-choice reaction time task probing attentional processes. In a baseline (slow, unrewarded) condition (72 trials), four empty circles (warning signals, arranged horizontally) first appear for 8s, after which one of them (the target) is coloured in. Participants are instructed to press the response key that directly corresponds to the position of the target. Following a response, the stimuli disappear from the screen and a fixed inter-trial interval of 2.5s follows. Speed and accuracy are emphasized equally. If the participant does not respond within 10s, the trial terminates. The baseline condition lasts approximately 15 min. A comparison condition (80 trials) with a fast event rate (1s) and incentives follows the baseline condition. The fast-incentive condition lasts approximately 5 min.	*Cognitive performance:* MRT, RTV from the baseline condition (more sensitive to ADHD; Kuntsi and Klein, 2012, Kuntsi et al., 2013). *ERPs*: P3 (attentional allocation) from the baseline condition.

4.3.5 Statistical analyses

4.3.5.1 Multivariate sibling-data model fitting

Sibling-data model fitting was accomplished by structural equation modelling (SEM) analyses using the OpenMx package in R (Boker et al., 2011). Since siblings share on average 50% of their segregating genes and 100% of the common environment, we can decompose the variance/covariance of traits into contributions of familial influences (the combined effects of shared genetic and shared environmental effects) and non-familial influences (individual-specific effects and possible measurement error) (Kuntsi et al., 2010, Cheung et al., 2012). Sibling-pair data allow us to derive: phenotypic correlations in each sibling, e.g., correlation between IQ and ADHD, constrained across birth order; cross-sibling/within-trait correlations, e.g., correlation between sibling 1 and sibling 2 for IQ; and cross-sibling/cross-trait correlations, constrained such that, for example, correlations between IQ in sibling 1 and ADHD in sibling 2 equals the correlation of IQ in sibling 2 and ADHD in sibling 1. The cross-sibling/within-trait and the cross-sibling/cross-trait correlations allow to estimate, respectively, the familial variance of a trait and the familial overlap between traits. Given the selected nature of this sample (selection of ADHD probands), ADHD status was included in all models with its parameters fixed to population-known values, based on previous evidence and consistent with our previous work (Cheung et al., 2012, Frazier-Wood et al., 2012, James et al., 2016, Kuntsi et al., 2010): the cross-sibling/within-trait correlation (correlation between siblings in each pair) was fixed to 0.40 (Chang et al., 2013, Larsson et al., 2014); the familiality to 0.40 (representing 80% genetic variance in case of null shared environmental effects) (Larsson et al., 2013); and prevalence of 5% (Willcutt, 2012) (z score set at 1.64). For further explanation of this approach see Appendix C and Rijsdijk and colleagues (2005). A liability threshold model framework, which assumes that the liability of ADHD is underpinned by a normally distributed continuum of risk (Rijsdijk and Sham, 2002, Rijsdijk et al., 2005), was used to account for the fact that ADHD was measured as present/absent. Model-fitting analyses were performed with raw data maximum likelihood estimation incorporating all available data points (thus allowing no listwise/pairwise deletion when data in sibling pairs were missing).

4.3.5.2 Preliminary analyses and variable selection

Preliminary constrained correlation bivariate models between ADHD and 22 cognitive-ERP variables extracted from our large cognitive-neurophysiological battery (sensitive to ADHD-control differences in this sample; Cheung et al., 2016, Michelini et al., 2016a, Cheung et al., 2017) were carried out to reduce the number of variables included in multivariate models. This

variable selection step was necessary due to the limit in the number of variables that can be included in multivariate SEM (Kuntsi et al., 2010, Loken et al., 2014). A phenotypical association with ADHD, and an evidence of familial effects, are prerequisites to any familial overlap between two variables. As such, cognitive-ERP variables were only included if they had (1) a phenotypic correlation with ADHD above the threshold of 0.20, corresponding to modest-to-large effect sizes (Cohen, 1988), and (2) significant cross-sibling/within-trait correlations, indicating similarity between siblings (Table S4.1, Appendix C).

Following preliminary analyses, nine variables were included with ADHD status in multivariate models: IQ, DSF, DSB, ERN (Figure S4.2, Appendix C) and congruent errors (CongE) from the arrow flanker task, NoGo-P3 (Figure S4.3, Appendix C) and OE from the CPT-OX, and MRT and RTV from the Fast task (baseline condition) (Table S4.2, Appendix C). ERN, NoGo-P3 and MRT were transformed to normality using square root, while RTV was log-transformed. IQ, DSF and DSB residuals were normally distributed. These measures were included as continuous variables. OE and CongE were highly skewed and could not be normalised using any transformation methods. They were therefore modelled as ordinal using 3 and 4 equal-sized categories, respectively. Age and sex were controlled for in all analyses as is standard practice for family model-fitting studies (McGue and Bouchard, 1984), by regressing out age and sex effects from continuous variables (before transforming to normality) and estimating age and sex effects on the mean for ordinal variables.

4.3.5.3 Cholesky and factor models

A multivariate Cholesky decomposition (Rijsdijk and Sham, 2002) was used to decompose the variance/covariance structure of the cognitive-ERP variables and ADHD into familial and non-familial influences. The correlated factors solution of this decomposition yielded familial and non-familial correlation matrices between all variables, which provide the degree of overlap between aetiological influences between two variables at a time (e.g., IQ and ADHD). We examined the aetiological factor structure underlying cognitive-ERP variables and ADHD in a more parsimonious model, following a two-step approach employed in previous work (Kuntsi et al., 2010, Frazier-Wood et al., 2012). Firstly, the derived familial and non-familial correlations between the nine cognitive-ERP variables were used as input to two separate exploratory factor analyses (EFAs) in R to extract the factor structure (Appendix C). Separate EFAs were carried out on the familial and non-familial correlations between the nine cognitive-ERP variables. This allowed detection of possible differences between the familial and non-familial effects on the number of extracted factors or in how they load on variables. Three factors with an eigenvalue

>1 were identified in both EFAs (Figure S4.1, Appendix C). Each factor explained >10% of the total variance in either EFA (Table S4.3, Appendix C). Since cognitive-ERP variables mapped onto cognitive processes which are likely to be interrelated (Kovas and Plomin, 2006, Jewsbury et al., 2016), we allowed the extracted factors to correlate by applying an oblique (oblimin) rotation (Gerbing and Hamilton, 1996, Widaman, 1993).

Secondly, we specified the three factors, their correlations and loadings (Table S4.3, Appendix C) separately for familial and non-familial influences in a confirmatory 3-factor model, including also ADHD, using OpenMx. Familial and non-familial paths from the extracted common factors were specified for each variable from the factor with strongest loading in the EFAs, while ADHD and its fixed familial and non-familial influences were modelled separately (Figure 4.1). Familial common paths on DSF and DSB, as well as non-familial common paths on MRT and RTV, were constrained to be equal for model identification purposes. Correlation paths were specified among each factor loading on cognitive-ERP measures and ADHD. The residual variance of cognitive-ERP variables not accounted for by common factors was measured by variable-specific familial and non-familial paths. For comparisons with other models see Table S4.4 (Appendix C).

4.4 Results

4.4.1 Phenotypic correlations

Phenotypic correlations between cognitive-ERP variables and ADHD were all significant, with positive correlations ranging from 0.17 to 0.88 and negative correlations from -0.19 to -0.39 (Table 4.3). The only non-significant correlation was between ERN and DSF (r_{Ph}=0.12, CIs: -0.01; 0.27). ADHD showed moderate negative correlations with IQ, DSF, DSB, ERN, NoGo-P3, and moderate positive correlations with MRT, RTV, OE and CongE.

4.4.2 Multivariate Cholesky decomposition

Familial correlations of ADHD with IQ, DSB, RTV, OE and CongE were significant and moderate-to-large, and moderate but non-significant with DSF, ERN, NoGo-P3 (Table 4.3). Non-familial correlations of ADHD with IQ, ERN, NoGo-P3, MRT, RTV, OE and CongE were modest and significant, while the correlations of ADHD with DSF and DSB were small and non-significant.

Table 4.3. Phenotypic, familial and non-familial correlations between study variables

Phenotypic	**IQ**	**DSF**	**DSB**	**ERN**	**NoGo-P3**	**MRT**	**RTV**	**OE**	**CongE**	**ADHD**
IQ	1									
DSF	**0.40 (0.30;0.50)**	1								
DSB	**0.41 (0.32;0.51)**	**0.51 (0.43;0.58)**	1							
ERN	**0.16 (0.04;0.28)**	0.12 (-0.00;0.27)	**0.17 (0.05;0.27)**	1						
NoGo-P3	**0.13 (0.02;0.25)**	**0.20 (0.08;0.28)**	**0.18 (0.07;0.31)**	**0.23 (0.13;0.34)**	1					
MRT	**-0.38 (-0.47;-0.27)**	**-0.19 (-0.30;-0.07)**	**-0.23 (-0.33;-0.11)**	**-0.24 (-0.35;-0.13)**	**-0.28 (-0.38;-0.17)**	1				
RTV	**-0.36 (-0.45;-0.26)**	**-0.16 (-0.28;-0.05)**	**-0.24 (-0.35;-0.13)**	**-0.30 (-0.38;-0.18)**	**-0.23 (-0.34;-0.12)**	**0.88 (0.85;0.89)**	1			
OE	**-0.33 (-0.44;-0.20)**	**-0.18 (-0.29;-0.05)**	**-0.25 (-0.37;-0.12)**	**-0.36 (-0.45;-0.22)**	**-0.31 (-0.42;-0.20)**	**0.35 (0.23;0.46)**	**0.37 (0.23;0.53)**	1		
CongE	**-0.21 (-0.33;-0.10)**	**-0.26 (-0.37;-0.14)**	**-0.20 (-0.32;-0.08)**	**-0.39 (-0.49;-0.27)**	**-0.30 (-0.42;-0.18)**	**0.32 (0.20;0.43)**	**0.33 (0.23;0.45)**	**0.37 (0.21;0.48)**	1	
ADHD	**-0.37 (-0.46;-0.25)**	**-0.21 (-0.32;-0.08)**	**-0.27 (-0.39;-0.15)**	**-0.24 (-0.37;-0.10)**	**-0.25 (-0.36;-0.13)**	**0.33 (0.20;0.44)**	**0.42 (0.29;0.52)**	**0.34 (0.20;0.46)**	**0.32 (0.18;0.44)**	1

Familial	IQ	DSF	DSB	ERN	NoGo-P3	MRT	RTV	OE	CongE	ADHD
IQ	1									
DSF	**0.50 (0.04;0.82)**	1								
DSB	**0.58 (0.32;0.81)**	**0.83 (0.61;0.98)**	1							
ERN	0.31 (-0.01;0.28)	0.08 (-0.36;0.49)	0.28 (-0.18;0.73)	1						
NoGo-P3	0.17 (-0.99;0.53)	0.27 (-0.15;0.63)	0.25 (-0.19;0.70)	0.12 (-0.49;0.59)	1					
MRT	**-0.65 (-0.88;-0.37)**	-0.29 (-0.59;0.05)	**-0.60 (-0.90;-0.24)**	**-0.51 (-0.94;-0.07)**	-0.28 (-0.65;0.21)	1				
RTV	**-0.66 (-0.94;-0.41)**	-0.26 (-0.60;0.10)	**-0.56 (-0.90;-0.16)**	**-0.52 (-0.97;-0.05)**	-0.18 (-0.61;0.35)	**0.95 (0.87;0.99)**	1			
OE	**-0.67 (-0.98;-0.29)**	**-0.41 (-0.82;-0.01)**	**-0.48 (-0.95;-0.02)**	**-0.72 (-0.97;-0.18)**	-0.36 (-0.79;0.25)	**0.50 (0.02;0.90)**	0.49 (-0.01;0.91)	1		
CongE	-0.25 (-0.63;-0.19)	-0.23 (-0.60;0.27)	-0.30 (-0.77;0.23)	**-0.69 (-0.97;-0.14)**	-0.45 (-0.84;0.20)	0.40 (-0.18;0.82)	**0.52 (0.30;0.91)**	**0.48 (0.05;0.94)**	1	
ADHD	**-0.38 (-0.63;-0.09)**	-0.30 (-0.60;0.05)	**-0.52 (-0.66;-0.16)**	-0.35 (-0.83;0.14)	-0.37 (-0.81;0.09)	0.33 (-0.04;0.69)	**0.45 (0.07;0.82)**	**0.60 (0.13;0.93)**	**0.56 (0.06;0.99)**	1

Non-familial	IQ	DSF	DSB	ERN	NoGo-P3	MRT	RTV	OE	CongE	ADHD
IQ	1									
DSF	**0.31 (0.16;0.45)**	1								
DSB	**0.32 (0.16;0.46)**	**0.32 (0.17;0.46)**	1							
ERN	0.09 (-0.06;0.24)	0.14 (-0.02;0.31)	0.12 (-0.04;0.28)	1						
NoGo-P3	0.12 (-0.05;0.28)	0.16 (-0.01;0.32)	0.15 (-0.03;0.31)	**0.26 (0.10;0.42)**	1					
MRT	**-0.21 (-0.35;-0.04)**	-0.13 (-0.29;0.04)	-0.05 (-0.21;0.12)	-0.15 (-0.31;0.02)	**-0.29 (-0.43;-0.12)**	1				
RTV	**-0.20 (-0.35;-0.03)**	-0.12 (-0.29;0.05)	-0.11 (-0.25;0.05)	**-0.22 (-0.37;-0.06)**	**-0.26 (-0.42;-0.09)**	**0.85 (0.80;0.89)**	1			
OE	-0.13 (-0.33;0.06)	-0.06 (-0.25;0.14)	-0.15 (-0.33;0.04)	**-0.25 (-0.43;-0.03)**	**-0.28 (-0.47;-0.10)**	**0.30 (0.11;0.47)**	**0.36 (0.15;0.51)**	1		
CongE	**-0.20 (-0.38;-0.04)**	**-0.29 (-0.46;-0.11)**	-0.17 (-0.33;0.00)	**-0.30 (-0.46;-0.13)**	**-0.24 (-0.43;-0.07)**	**0.30 (0.15;0.47)**	**0.30 (0.14;0.45)**	**0.30 (0.16;0.52)**	1	
ADHD	**-0.36 (-0.52;-0.18)**	-0.13 (-0.31;0.05)	-0.14 (-0.31;0.05)	**-0.20 (-0.38;-0.01)**	**-0.20 (-0.36;-0.01)**	**0.32 (0.14;0.49)**	**0.40 (0.22;0.57)**	**0.22 (0.03;0.45)**	**0.24 (0.02;0.44)**	1

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CongE, errors in the congruent condition of the flanker task; DSB, digit span backward; DSF, digit span forward; ERN, error-related negativity amplitude from the flanker task; IQ, intelligence quotient; MRT, mean reaction time from the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued continuous performance test; OE, omission errors from the cued continuous performance test; RTV, reaction time variability from the Fast task.

Note: Significant (p<0.05) correlations are indicated in bold.

4.4.3 Multivariate factor model

Three familial and three non-familial factors emerged from EFAs, explaining the association between the nine cognitive-ERP variables (Figure S4.1, Appendix C). This factor structure informed the confirmatory factor model, which provided the best fit to the data (Table S4.4, Appendix C). The first familial factor (cF_1) loaded onto IQ, MRT and RTV; the second factor (cF_2) onto DSF and DSB; and the third factor (cF_3) onto ERN, NoGo-P3, OE and CongE (Figure 4.1). The three familial factors accounted for most of the familial variance on cognitive-ERP measures, as variable-specific familial influences were in general low and non-significant, apart from those on DSF (0.13; 30% of familial variance) and NoGo-P3 (0.21; 81% of familial variance) (Table 4.4). The familial factors showed high inter-correlations and moderate-to-high correlations with familial influences on ADHD (Figure 4.1).

The factor structure of non-familial influences resembled that of familial influences, except for IQ which loaded on the same factor capturing DSF and DSB (Figure 4.1). The majority of the non-familial variance of most cognitive-ERP measures was not explained by these three factors (cNf_{1-3}), but by specific influences, apart from MRT and RTV which were more strongly influenced by a common non-familial factor (cNf_1) (Table 4.4). The non-familial factors showed moderate-to-high inter-correlations and moderate correlations with non-familial influences on ADHD. The phenotypic correlation between each cognitive-ERP variable and ADHD was explained to a similar extent by shared familial and non-familial factors (Table S4.5, Appendix C).

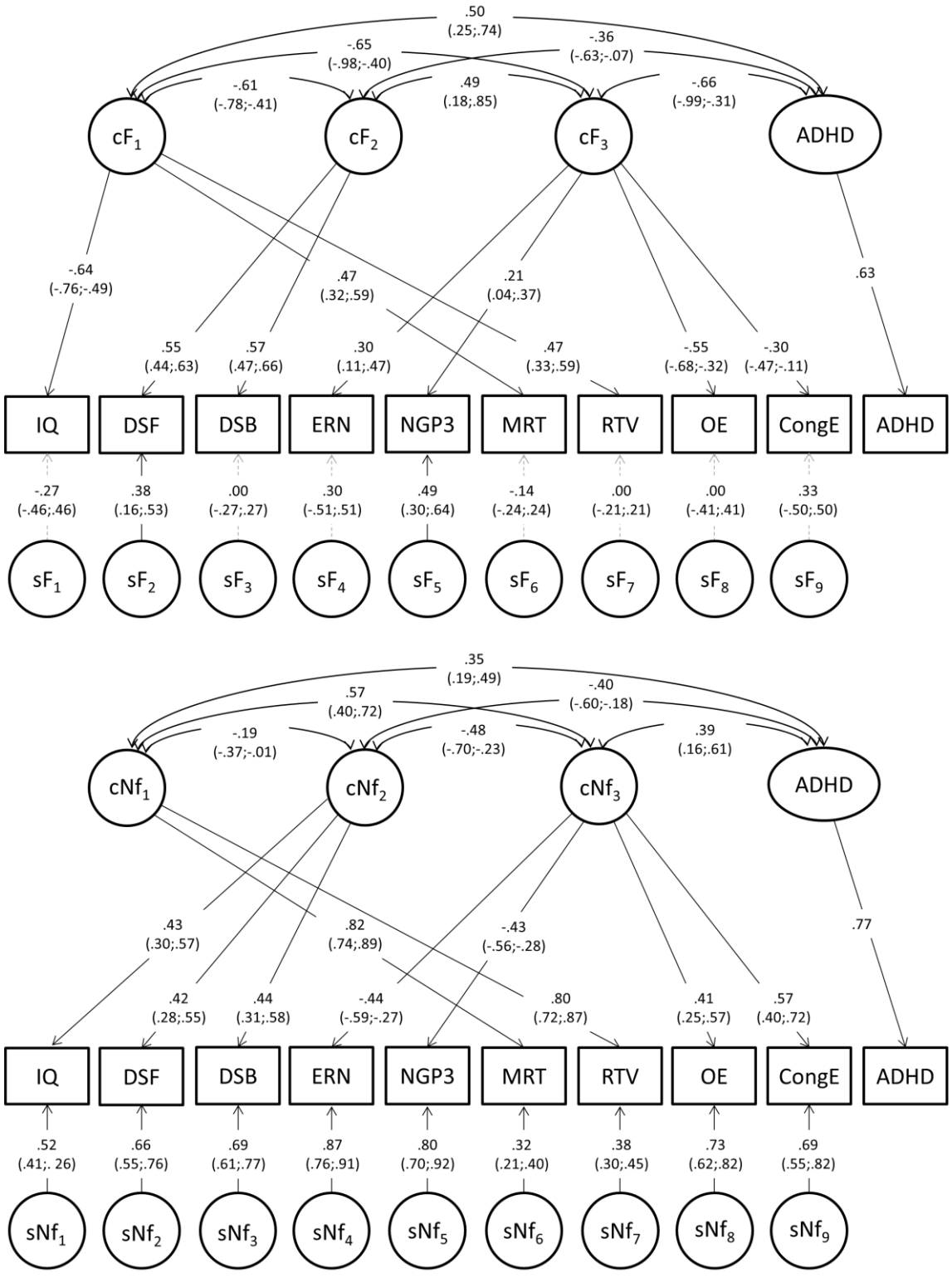

Figure 4.1. *Confirmatory Factor model between cognitive-ERP variables and ADHD*
Notes: Significant (p<.05) parameters are indicated with solid lines and nonsignificant parameters with dotted grey lines.

Table 4.4. Factor structure and standardised familial (F) and non-familial (Nf) variance of cognitive-ERP measures, also split up by contribution of each factor and of specific (residual) effects, with 95% confidence intervals in brackets

	Total	Common F1	Common F2	Common F3	Specific
	Familial influences				
IQ	**.49 (.38;.59)**	**.41 (.24;.57)**			.08 (.00;.24)
DSF	**.43 (.31;.54)**		**.30 (.20;.40)**		**.13 (.02;.24)**
DSB	**.33 (.22;.43)**		**.33 (.22;.43)**		.00 (.00;.00)
ERN	**.17 (.02;.32)**			**.09 (.01;.22)**	.08 (.00;.21)
NoGo-P3	**.26 (.11;.40)**			**.05 (.01;.14)**	**.21 (.08;.34)**
MRT	**.24 (.12;.37)**	**.22 (.18;.34)**			.02 (.00;.06)
RTV	**.22 (.10;.35)**	**.22 (.10;.35)**			.00 (.00;.00)
OE	**.30 (.10;.45)**			**.30 (.10;.47)**	.00 (.00;.00)
CongE	**.20 (.05;.39)**			**.09 (.01;.22)**	.11 (.00;.25)
	Non-familial influences				
IQ	**.51 (.41;.62)**		**.19 (.09;.33)**		**.32 (.19;.30)**
DSF	**.57 (.46;.69)**		**.17 (.08;.30)**		**.40 (.27;.52)**
DSB	**.68 (.57;.78)**		**.20 (.09;.33)**		**.48 (.37;.58)**
ERN	**.83 (.68;.98)**			**.19 (.08;.31)**	**.64 (.49;.80)**
NoGo-P3	**.74 (.61;.89)**			**.18 (.08;.31)**	**.56 (.42;.72)**
MRT	**.76 (.63;.88)**	**.67 (.54;.79)**			**.10 (.04;.15)**
RTV	**.78 (.65;.89)**	**.64 (.53;.76)**			**.14 (.08;.19)**
OE	**.70 (.55;.90)**			**.16 (.06;.32)**	**.54 (.38;.68)**
CongE	**.80 (.61;.95)**			**.32 (.16;.52)**	**.48 (.31;.67)**

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; Common F1-F3, the standardised variance of each variable explained by familial and non-familial factors; CongE, errors in the congruent condition of the flanker task; DSB, digit span backward; DSF, digit span forward; ERN, error-related negativity amplitude from the flanker task; IQ, intelligence quotient; MRT, mean reaction time from the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued continuous performance test; OE, omission errors from the cued continuous performance test; RTV, reaction time variability from the Fast task; Specific, measure-specific standardised variance due to familial and non-familial influences; Total, total standardised variance of each variable due to familial and non-familial influences.
Note: Significant (p<0.05) estimates are indicated in bold.

4.5 Discussion

This study represents the first comprehensive investigation to date, using a broad range of cognitive-performance and brain activity (EEG) measures, into the aetiology underlying cognitive-neurophysiological impairments in ADHD that has persisted from childhood to adolescence and early adulthood. We identified three familial and three non-familial factors underlying the association between impairments in these measures and ADHD. The familial factors captured: (1) response speed (MRT) and variability (RTV), and IQ; (2) short-term (DSF) and working (DSB) memory; and (3) sustained attention (OE, CongE), error processing (ERN) and, to a smaller extent, response inhibition (NoGo-P3). Familial influences on ADHD overlapped strongly with both the first and third factors; but only moderately with the memory (second) factor. The same number of factors emerged for non-familial influences, with the only exception that IQ clustered with memory rather than RT measures. These findings identify multiple partially separable aetiological processes that underlie cognitive-neurophysiological impairments in persistent ADHD, extending our understanding of the aetiological pathways to widespread cognitive and brain dysfunction in ADHD in adolescence and adulthood.

Our results show substantial shared familial influences between cognitive-neurophysiological impairments and ADHD in adolescents and young adults. The factor model further indicates that the association between these impairments and ADHD ($r_{cF1\text{-}ADHD}$=.50; $r_{cF2\text{-}ADHD}$=-.36; $r_{cF3\text{-}ADHD}$=-.66) may underlie multiple familial processes. The factor structure for familial effects pointed to a separation between a factor capturing IQ and RT performance (cF_1), a factor capturing memory performance (cF_2), and a factor capturing accuracy (number of errors) and brain activity of inhibitory/error-detection processes (cF_3). The separation between factors indicates that the co-occurring presence of impairments captured by the same factor could be largely explained by shared familial influences. For example, the finding that one familial factor captured both IQ and RT performance indicates a strong familial association between these measures (more than with other measures) in adolescents and adults. Conversely, impairments that are captured by two separate factors may be driven by at least partially separate familial pathways. A dissociation of this kind is shown for memory and RT performance, indicating that impairments in these processes may result from partly independent aetiological pathways. In addition, to our knowledge, this is the first family model-fitting study that simultaneously investigated multiple cognitive and brain measures to obtain a deeper understanding of ADHD. Our results provide new insights into how cognitive-performance impairments (omission and congruent errors) are aetiologically associated with neural processes of error detection (ERN) and response inhibition

(NoGo-P3), as these four measures clustered in one factor. As such, the aetiological factors underlying atypical brain activity of inhibitory and error-detection processes may overlap with those linked to task accuracy indices of sustained attention deficits. The familial factor capturing these four measures (cF_3) also overlapped with two thirds of the familial influences on ADHD ($r_{cF3\text{-}ADHD}$=-.66), indicating a strong aetiological association between this cognitive-EEG factor and the disorder.

More generally, our results point to a multifactorial structure of impairments in cognitive and brain function in ADHD, in line with models on ADHD proposing that cognitive and brain dysfunction in the disorder may arise from multiple pathways (Castellanos and Proal, 2012, Halperin and Schulz, 2006, Johnson, 2012). This multifactorial structure may explain the observed individual differences in cognitive profiles that exist among adolescents and adults with ADHD, who may display various degrees of impairments in different cognitive domains (Mostert et al., 2015). A possible clinical implication of these findings is that future efforts to implement new treatments for ADHD could consider including various intervention components, each targeting these different cognitive processes. Given the partial aetiological dissociation between the identified cognitive clusters in ADHD, impairments in these factors may have different roles in relation to ADHD pathophysiology. For example, it may be that only some impairments represent mediators lying on the causal pathways to ADHD, while others may only represent associated characteristics (Kendler and Neale, 2010). This partial dissociation between these processes should be considered in future research efforts aiming to examine the role of these impairments in the pathways to ADHD.

Our study provides new evidence on the aetiological processes underlying impairments in cognitive and brain function in ADHD adolescence and adulthood. These findings are largely consistent with two earlier findings in childhood (Kuntsi et al., 2010, Frazier-Wood et al., 2012). First, the separation of the factor capturing RT performance from the factor capturing response-accuracy measures is consistent with the separation between one factor capturing MRT/RTV from another factor capturing omission/commission errors found in a multi-site study which included data from the sample of the current study in childhood (Kuntsi et al., 2010). Second, the separation between aetiological influences on RT and memory performance in adolescents and young adults is further consistent with another study in children where RTV and working memory were captured by two different factors (Frazier-Wood et al., 2012). Differences between this analysis and previous childhood studies were also observed in the extent of the aetiological overlap among IQ, RT performance and ADHD. In the present study, IQ and RTV/MRT

were captured by a single familial factor (cF_1) highly correlated with ADHD, suggesting substantial overlap in familial variance between these measures. The previous analyses in childhood, however, found a separation of genetic/familial influences on IQ from influences on ADHD and other cognitive impairments (Wood et al., 2010, Wood et al., 2011, Rommelse et al., 2008c), suggesting that IQ may represent a separate process. For example, two studies in children reported that the majority (66-81%) of the genetic/familial influences on IQ were independent of those shared between RT impairments and ADHD (Wood et al., 2010, Wood et al., 2011). Previous analyses on this sample, however, also indicate that lower IQ, both in childhood and at follow-up, predicted ADHD persistence (Cheung et al., 2015, Cheung et al., 2016). As such, one possible explanation for the substantial overlap in familial influences between IQ and ADHD in this older age group is that IQ is a potential moderator of ADHD outcome from childhood to adolescence and adulthood. Future longitudinal analyses are needed to elucidate these developmental associations between ADHD and impairments in cognitive and neural processes throughout the development.

It is of interest to note that the separation of familial factors was similar to the distinct processes underlying ADHD persistence and remission previously reported in phenotypic analyses on this sample (Cheung et al., 2016, Michelini et al., 2016a). Specifically, IQ/RT and attention/error-processing measures, here captured by two factors with substantial familial sharing with ADHD, were associated with severity and persistence of ADHD in phenotypic analysis (Cheung et al., 2016, Michelini et al., 2016a). One possible prediction from these findings is that, in individuals with persistent ADHD, these two factors may jointly contribute to the severity of ADHD and the presence of cognitive-neurophysiological impairments. Conversely, short-term and working memory (here captured by a familial factor that was only moderately overlapping with ADHD) and the response-inhibition NoGo-P3 (here mostly influenced by specific factors not shared with other variables or ADHD) were not sensitive to ADHD persistence/remission in our previous work, in that impairments in these measures did not distinguish individuals with persistent and remitted ADHD (Cheung et al., 2016). As such, we can hypothesise that impairments in short-term/working memory and in brain activity of inhibition control may reflect separate enduring processes in ADHD associated with persistence of impairments in cognitive and brain function - regardless of severity of ADHD symptoms and impairment.

Non-familial influences on ADHD showed moderate overlap with all three non-familial factors. Of note, the common factor cNf_1 captured almost all of the non-familial variance shared between ADHD and RT measures, as limited residual variance was not shared with the disorder.

Conversely, the non-familial variance of IQ and short-term/working memory (cNf_2), and of sustained attention and inhibitory/error-detection processes (cNf_3) was largely measure-specific and not shared with ADHD. Non-familial influences include individual-specific environmental factors, representing any differences in the environment between siblings, and may include the effects of any treatment for ADHD. A possible prediction is that non-pharmacological interventions, for example cognitive training, aimed at alleviating ADHD symptoms may be more effective if they target RT rather than memory or response-accuracy processes. This prediction is in line with evidence suggesting that RTV may be more malleable than higher-level processes (Kuntsi et al., 2009) and may explain the low efficacy of treatments targeting working-memory impairments on ADHD (Cortese et al., 2015).

The comprehensive investigation of impairments in cognitive and brain function, with both cognitive-performance and brain-activity measures, and application of sibling model-fitting analyses in a clinical sample are strengths of the current study. One limitation is that sibling data only allow the investigation of familial and non-familial effects, but cannot directly estimate the contribution of genetic factors. However, since previous research suggests a limited role of shared-environmental influences on either ADHD (Burt et al., 2012, Nikolas and Burt, 2010) or cognitive-neurophysiological markers (Anokhin et al., 2008, Kuntsi et al., 2013), the familial overlap between ADHD and such markers is expected to largely reflect genetic influences. Future twin studies are required to confirm this matter. In addition, the age range was wide in our sample. To allow the inclusion children with combined-type ADHD and their siblings at initial assessment, a wide age range was needed for adequate sample size and power for sibling analyses. This prevented us from examining whether the aetiological structure of impairments in ADHD may vary with age, as stratifying the analyses by age would have resulted in small samples for sibling analyses. Yet, since we controlled for age in all analyses, we can rule out that our results are confounded by age effects. Future studies using more restricted age ranges should examine these issues.

In conclusion, by using a multivariate approach on a broad range of cognitive and neurophysiological measures, we have identified, for the first time in adolescents and young adults with ADHD, three partially separable factors that captured substantial familial influences (36-66%) on ADHD and impairments in cognitive and brain function, extending current knowledge from childhood to later development. The familial processes underlying both slower and more variable RTs and lower IQ in adolescents and young adults with ADHD may be partially distinct from familial influences on memory dysfunction and on impairments in sustained

attention and brain activity of inhibitory/error-detection processes. These partially distinct aetiological pathways may underlie dysfunctional brain networks which are, in turn, associated with impaired cognition and behaviour in the disorder. Future efforts should examine the developmental trajectories of these aetiological pathways, and test treatment effects on these partially separate cognitive-neurophysiological factors, which would refine causal models of the disorder and point to sensitive targets for interventions.

CHAPTER 5 - Disorder-specific and shared neurophysiological impairments of attention and inhibition in women with ADHD and women with bipolar disorder

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ORIGINAL ARTICLE

Disorder-specific and shared neurophysiological impairments of attention and inhibition in women with attention-deficit/hyperactivity disorder and women with bipolar disorder

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Background. In adults, attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) have certain overlapping symptoms, which can lead to uncertainty regarding the boundaries of the two disorders. Despite evidence of cognitive impairments in both disorders separately, such as in attentional and inhibitory processes, data on direct comparisons across ADHD and BD on cognitive–neurophysiological measures are as yet limited.

Method. We directly compared cognitive performance and event-related potential measures from a cued continuous performance test in 20 women with ADHD, 20 women with BD (currently euthymic) and 20 control women.

Results. The NoGo-N2 was attenuated in women with BD, reflecting reduced conflict monitoring, compared with women with ADHD and controls (both $p < 0.05$). Both ADHD and BD groups showed a reduced NoGo-P3, reflecting inhibitory control, compared with controls (both $p < 0.05$). In addition, the contingent negative variation was significantly reduced in the ADHD group ($p = 0.05$), with a trend in the BD group ($p = 0.07$), compared with controls.

Conclusions. These findings indicate potential disorder-specific (conflict monitoring) and overlapping (inhibitory control, and potentially response preparation) neurophysiological impairments in women with ADHD and women with BD. The identified neurophysiological parameters further our understanding of neurophysiological impairments in women with ADHD and BD, and are candidate biomarkers that may aid in the identification of the diagnostic boundaries of the two disorders.

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Key words: Attention, attention-deficit/hyperactivity disorder, bipolar disorder, conflict monitoring, event-related potentials, inhibitory control.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) are common psychiatric conditions in adults, affecting around 2–4% and 1–2% of the adult population, respectively (Merikangas *et al.* 2011; Willcutt, 2012). Although ADHD and BD represent distinct conditions, their diagnostic formulations present certain areas of symptomatic overlap. In adults, ADHD may be manifest with some symptoms common to mania/hypomania, such as distractibility, psychomotor restlessness and talkativeness (Skirrow *et al.* 2012; Asherson *et al.* 2014). Additionally, both disorders are associated with features of mood dysregulation, such as irritability and emotional lability (Skirrow *et al.* 2012, 2014; GL Kitsune *et al.* unpublished observations). Of note, ADHD symptoms are chronic and trait-like, while BD symptoms of mania and depression tend to occur for a distinct period of time (Asherson *et al.* 2014). Yet, individuals with BD may still show residual symptoms of distractibility and mood dysregulation (overlapping with ADHD), and residual cognitive and functional impairments between episodes (Torres *et al.* 2007; Henry *et al.* 2013). Importantly, symptomatic similarities can result in uncertainty regarding the boundaries of the two disorders, and difficulties in distinguishing between the two disorders in some patients, which in turn may result in inappropriate treatment decisions (Asherson *et al.* 2014).

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Adults with ADHD or BD may display similar cognitive impairments. For example, both ADHD and euthymic BD are associated with poor accuracy in attentional and inhibitory processing tasks (Robinson *et al.* 2006; McLoughlin *et al.* 2010; Torralva *et al.* 2011) and increased reaction time variability (RTV), which may reflect short-term fluctuations in attentional performance (Brotman *et al.* 2009; Kuntsi *et al.* 2010; Kuntsi & Klein, 2012). Comparative studies across ADHD and BD, using identical measures, may aid in the identification of attentional and inhibitory deficits underlying overlapping symptoms and functional impairment, yet empirical data are currently limited.

The investigation of neurophysiological processes with event-related potentials (ERPs) provides a direct measure of covert brain activity underlying behavioural performance with millisecond temporal resolution, and may enable a sensitive comparison of cognitive profiles in ADHD and BD (Banaschewski & Brandeis, 2007; McLoughlin *et al.* 2014*a*). Several previous studies on attentional and inhibitory processing in ADHD have explored ERPs during the cued continuous performance test (CPT-OX), which involves presentation of cue, target (Go) and non-target (NoGo) stimuli and requires a response only when a target follows a cue (van Leeuwen *et al.* 1998; Banaschewski *et al.* 2004). A reduced fronto-central P3 has consistently been reported in response to NoGo stimuli (NoGo-P3) in children, adolescents and adults with ADHD compared with controls, reflecting abnormal inhibitory control (Valko *et al.* 2009; Doehnert *et al.* 2010; McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Tye *et al.* 2014). Attenuations in a parietal P3 after presentation of cue stimuli (Cue-P3) and in the subsequent contingent negative variation (CNV), a late negative potential before the occurrence of the next stimulus, have also been found in individuals with ADHD, reflecting impaired attentional orienting and response preparation, respectively (Doehnert *et al.* 2010; McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013), although case–control differences in these components have not been reported in all studies (Dhar *et al.* 2010; Skirrow, 2012). Differences between adults with ADHD and control adults are generally not found in other ERP components elicited by this task; such as the P3 in response to target (Go-P3), reflecting response execution, and the N2 to non-target stimuli (NoGo-N2), indexing conflict monitoring, which refers to the ability to monitor ongoing behaviour, detect conflict and adjust response selection (Yeung & Cohen, 2006; McLoughlin *et al.* 2010). N2 deflections are particularly elicited by high-conflict trials, such as non-target or incongruent stimuli, and are attenuated in ADHD individuals in paradigms inducing higher conflict-monitoring demands than the CPT-OX, such as flanker tasks, suggesting possible modulations of this component by task and stimuli (Barry *et al.* 2009; McLoughlin *et al.* 2009, 2014*b*).

In ERP studies, BD has been associated with attenuations in early sensory and attentional ERP components (e.g. mismatch negativity, P50 and P2) in auditory tasks (Hall *et al.* 2007; Jahshan *et al.* 2012; Cabranes *et al.* 2013; Swann *et al.* 2013). Reduced P3 enhancements to target stimuli have been reported in adults with BD in studies using a visual paradigm with standard, deviant and target conditions (Maekawa *et al.* 2013) and using an oddball paradigm (Hall *et al.* 2007), but not in all studies (Schulze *et al.* 2008; Bestelmeyer, 2012). Some evidence also indicates impairments in conflict monitoring in adults with BD, indexed by reduced N2 in response to target stimuli with an auditory oddball task (Ethridge *et al.* 2012) and reduced error-related negativity (ERN) in error responses (Morsel *et al.* 2014). Despite initial evidence that may suggest impairments in ERPs of attentional and inhibitory processing in BD, however, ERP data on these processes are limited, and no studies, to our knowledge, have used the CPT-OX.

Direct comparisons on cognitive performance and ERP measures in ADHD and BD are sparse. One study on adults with ADHD and adults with BD investigating ERP measures of reward processing found significant differences in the amplitude of a reward-sensitive P3, which was attenuated in ADHD but enhanced in BD participants compared with controls (Ibanez *et al.* 2012). However, no study to date has compared ERP components associated with attentional and inhibitory processing in both disorders using the CPT-OX. In addition, most studies of this kind, especially on ADHD, have used male samples because, among children, ADHD is more prevalent in males than in females, and very little is known about these processes in females. Yet, a similar prevalence of ADHD has been reported in both adult men and women (Faraone & Biederman, 2005; Das *et al.* 2012). Similarly, comparable gender ratios have been found for BD in adults (Pini *et al.* 2005).

The aim of the current study was to directly compare cognitive performance and ERP measures associated with attentional and inhibitory processing in ADHD and BD in adults. This study was conducted on an all-female sample, in order to match the groups on gender but also to explore the neglected area of ERP indices associated with these processes in females. Based on previous studies of male participants (McLoughlin *et al.* 2010; Albrecht *et al.* 2013; Doehnert *et al.* 2013), we predicted that women with ADHD would show reduced NoGo-P3, Cue-P3 and CNV, but normal NoGo-N2. Given the limited and mixed results in ERP studies of BD individuals and the lack of similar

studies using the CPT-OX, we adopted an exploratory approach for the BD group and for the comparison with ADHD.

Method

Sample

The sample for this study consisted of 60 adult women aged between 20 and 52 years, divided into three groups: 20 with ADHD, 20 with BD and 20 controls. Participants with ADHD were recruited from the National Adult ADHD Clinic at the Maudsley Hospital, where any female cases meeting inclusion criteria were considered for potential inclusion in the study. Participants with BD were recruited from the Maudsley Psychosis Clinic and a sample that had previously participated in another research study (Hosang *et al.* 2012). Control participants were recruited from the Mindsearch volunteer database maintained by the Institute of Psychiatry, King's College London, which comprises several thousand potential participants. Participants were randomly selected from all those meeting recruitment criteria for this study.

Diagnosis in the clinical groups was confirmed by checking medical records for details of diagnosis and psychiatric history, following Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (APA, 2000). All of the ADHD participants had a current combined-type diagnosis or a current inattentive-type diagnosis with sufficient symptoms of hyperactivity–impulsivity in childhood to meet a childhood combined-type diagnosis. Participants in the BD group had a diagnosis of BD type I, having experienced at least one manic episode in the past. Those who were experiencing a manic episode at the time of the assessment were excluded; all participants included in the BD group were currently euthymic. Exclusion criteria for all groups were drug or alcohol dependency in the last 6 months, autism, epilepsy, neurological disorders, brain injury, past electroconvulsive therapy, current involvement in another research trial likely to alter symptom severity, pregnancy or a limited proficiency in the English language. Individuals with ADHD and individuals with BD with a reported co-morbidity of both ADHD and BD were also excluded. Control participants, who reported a history of psychiatric disorders or who were taking psychiatric medication, were excluded from the study. Co-morbidity in the clinical groups and lack of psychiatric disorders in the control group were further assessed through clinical evaluations when participants underwent the cognitive–electroencephalographic (EEG) assessment for this study. Further details on the clinical assessment of this sample can be found elsewhere (GL Kitsune *et al.* unpublished observations). In brief, ADHD was excluded in the BD group after conducting the Diagnostic Interview for ADHD in Adults (DIVA v. 2.0; Kooij & Francken, 2007). BD was excluded in the ADHD group by checking for a history of past episodes of depression or hypomania/mania and evaluating current mood symptoms using the Altman Self-Rating Mania Scale (Altman *et al.* 1997) and the Beck Depression Inventory (Beck *et al.* 1996), and current and lifetime ever symptoms using the Young Mania Rating Scale (Young *et al.* 1978). The ADHD and BD groups did not differ significantly on any of the mood scales for current symptoms (GL Kitsune *et al.* unpublished observations).

All participants had normal or corrected-to-normal vision. Mean age did not differ by group ($F_{2,59} = 1.63$, $p = 0.21$), with a mean age of 37.40 (S.D. = 7.70) for the ADHD group, 40.30 (S.D. = 7.70) for the BD group and 36.7 (S.D. = 4.30) for the control group. Participants' intelligence quotients (IQs) were assessed with the Wechsler Abbreviated Scale of Intelligence, fourth edition (Wechsler, 1999) and did not differ between groups ($F_{2,58} = 1.37$, $p = 0.26$), with mean IQs of 104 (S.D. = 17.90) for ADHD, 108 (S.D. = 12.50) for BD and 112 (S.D. = 14.20) for control participants. Participants with ADHD were asked to stop taking any stimulant medication prescribed for their ADHD 48 h prior to the assessment. For ethical reasons, participants were not asked to stop taking mood stabilizers (70% of the BD group), anti-psychotic medication (40% of the BD group) or anti-depressants (7% of the ADHD group and 25% of the BD group) they had been prescribed. All participants were asked to refrain from caffeinated drinks and nicotine 2 h prior to the testing session. Ethical approval for the study was granted by the Camberwell St Giles Research Ethics Committee (approval number 11/LO/0438) and all participants provided informed consent.

Procedure and cognitive performance measures

Participants attended a single 4.5 h research session (including breaks) for cognitive–EEG assessment, IQ assessment and clinical interviews. The task was a CPT-OX, flanker version (Doehnert *et al.* 2008; McLoughlin *et al.* 2010, 2011). This is a cued-Go/NoGo task that probes attention, preparation and response inhibition or control. The task consists of 400 letter arrays formed of a centre letter with incompatible flankers on each side to increase difficulty for adults. Each letter array was presented for 150 ms with a stimulus onset asynchrony (SOA) of 1.65 s in a pseudo-randomized order at the centre of a computer monitor. The tasks involved the presentation of 80 cues (XOX) followed either by 40 Go (OXO) and 40 NoGo (XDX) stimuli, alternated with random letter sequences as distractors. Participants were instructed to

respond only to Cue-Go sequences by pressing a button as quickly as possible with the digit finger of their preferred hand, and to withhold the response in presence of a NoGo stimulus, of a Go not preceded by a cue (40 trials), or of any other irrelevant letters. The task was practised prior to task performance and lasted 11 min. The task followed a 2 × 3 min resting-state recording, and was run as first in a battery of three cognitive–EEG tasks.

Cognitive performance measures included target mean reaction time (MRT, i.e. mean latency of responding in ms after target onset), RTV (measured as standard deviation of target reaction time) and number of errors. MRT and RTV were calculated across correctly answered Go trials. Errors included omission errors (non-response to Go trials), total commission errors (response to cue, NoGo or distractor stimuli) and OXO-not-XOX commission errors (response to a Go not following a cue).

Electrophysiological recording and analysis

The EEG was recorded from a 62-channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling rate, impedances under 10 kΩ, and FCz as the recording reference. The electro-oculograms were recorded from electrodes above and below the left eye and at the outer canthi. The EEG data were analysed using Brain Vision Analyser 2.0 (Brain Products). Researchers were blind to group status during EEG pre-processing and analysis. Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and digitally filtered using Butterworth band-pass filters (0.1–30 Hz, 24 dB/octave). All trials were also visually inspected for electrical artefacts (due to electrical noise in the EEG recording) or obvious movement, and sections of data containing artefacts were removed manually. Ocular artefacts, corresponding to blink-related and vertical and horizontal eye movements, were identified using the infomax Independent Component Analysis algorithm (ICA; Jung *et al.* 2000), which allows for removal of the components associated with ocular artefacts by back-projection of all but those components. Sections of data with remaining artefacts exceeding ±100 μV in any channel or with a voltage step greater than 50 μV were automatically rejected. Baseline correction was performed using a 500-ms pre-stimulus reference period[1]†.

Stimulus-locked epochs (stimulus window from −200 to 1650 ms) were averaged based on three different response conditions: cue, Go and NoGo. Averages only included trials with correct responses (Go) or correctly rejected trials (NoGo and cue) and contained at least 20 artefact-free segments (see online Supplementary material for number of segments included in the ERP average by group). ERP measures were identified within the selected electrodes and latency windows for which effects were expected to be largest, based on previous studies (McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013) and verified against the topographic maps and the grand averages (Figs 1–3). ERPs were measured as the mean amplitude in the designated latency window. This approach has been adopted in previous similar studies (Groom *et al.* 2010; Tye *et al.* 2014), and has the advantage of being unaffected by latency variability (Luck, 2005). In cue trials, the P3 was measured at Pz between 300 and 650 ms, and the CNV at Cz between 1300 and 1650 ms. In NoGo trials, the N2 was measured at Fz between 175 and 325 ms, and the P3 at Cz between 250 and 550 ms. In Go trials, the P3 was measured at CPz between 250 and 500 ms. A clear N2 was not observed in Go trials, in line with other studies on tasks inducing a low-conflict-monitoring demand (Bokura *et al.* 2001; Gajewski & Falkenstein, 2013) and was not included into the analysis.

Statistical analyses

All participants were included in the analysis of cognitive performance data. Two ADHD participants were excluded from the ERP analysis of the Go condition due to having less than 20 artefact-free segments available for analysis.

Group differences on the reaction time measures were explored using univariate analyses of variance (ANOVAs), followed by *post-hoc t* tests. MRT and RTV had skewed distributions and were log-transformed with optimized minimal skew through the 'lnskew0' command in Stata (Stata Corp.). Performance accuracy was generally high as errors were rare, in line with previous studies on this task (McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013). Since distribution of errors was thus not normal and no transformations were successful, effects of group on these variables were entered into non-parametric analysis, using Kruskal–Wallis tests, followed by *post-hoc* Mann–Whitney *U* tests.

Group effects on ERP parameters were tested with separate ANOVAs, followed by *post-hoc t* tests. All ERP measures had normal distribution. We report both p values ($p < 0.05$ for significance and $p < 0.10$ for a trend) and effect sizes (Cohen's d) for comparisons of cognitive performance and ERP measures. Effect sizes were calculated using the difference in the means, divided by the pooled standard deviation,

† The notes appear after the main text.

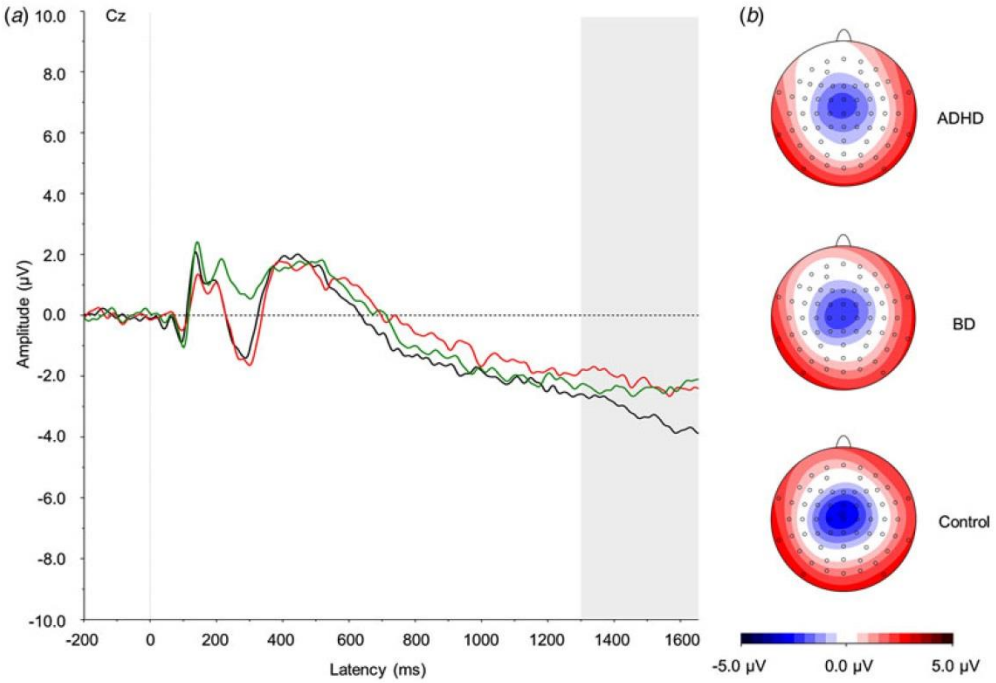

Fig. 1. (*a*) Grand average event-related potentials to cue stimuli at the Cz electrode, showing the contingent negative variation in the 1300–1650 ms window. ADHD, Attention-deficit/hyperactivity disorder (light grey; red online); BD, bipolar disorder (mid grey; green online). Controls are shown in black. (*b*) Topographic maps for each group. For a colour figure, see the online version.

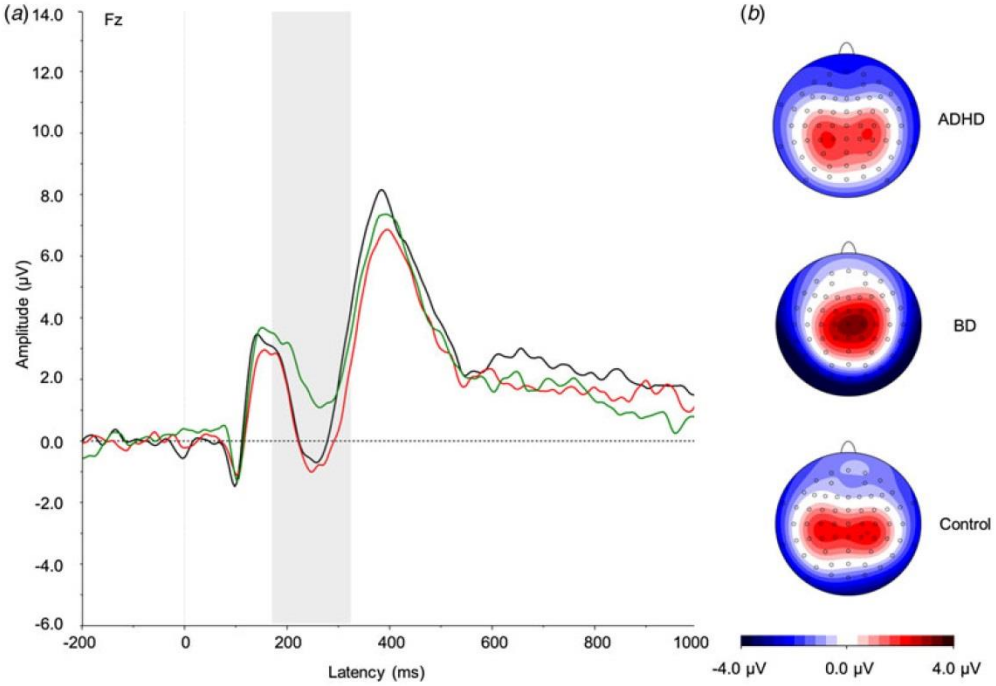

Fig. 2. (*a*) Grand average event-related potentials to NoGo stimuli at the Fz electrode, showing the NoGo-N2 in the 175–325 ms window. ADHD, Attention-deficit/hyperactivity disorder (light grey; red online); BD, bipolar disorder (mid grey; green online). Controls are shown in black. (*b*) Topographic maps for each group. For a colour figure, see the online version.

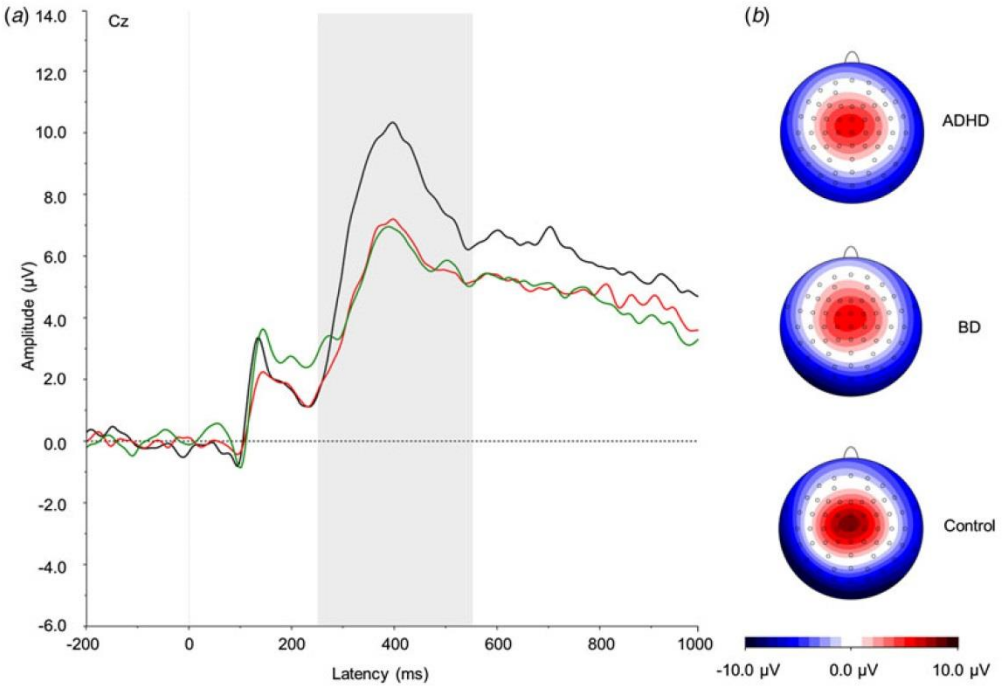

Fig. 3. (*a*) Grand average event-related potentials to NoGo stimuli at the Cz electrode, showing the NoGo-P3 in the 250–550 ms window. ADHD, Attention-deficit/hyperactivity disorder (light grey; red online); BD, bipolar disorder (mid grey; green online). Controls are shown in black. (*b*) Topographic maps for each group. For a colour figure, see the online version.

where $d = 0.20$ constitutes a small effect, $d = 0.50$ a medium effect and $d = 0.80$ a large effect (Cohen, 1988).

Ethical standards

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Cognitive performance measures

A trend-level effect of group emerged for RTV ($F_{2,57} = 2.67$, $p = 0.08$). *Post-hoc* analyses revealed a significant difference between the BD and control groups ($p = 0.03$) and a trend-level difference between the ADHD and control groups ($p = 0.06$) on RTV, both with medium effect sizes (Table 1), but no differences between the ADHD and BD groups ($p = 0.93$). Groups did not differ on MRT ($F_{2,57} = 1.47$, $p = 0.24$).

Trend-level effects emerged on the number of total commission errors ($H_2 = 4.96$, $p = 0.08$) and omission errors ($H_2 = 4.74$, $p = 0.09$). *Post-hoc* analyses indicated that participants with ADHD made significantly more commission ($p = 0.03$) and omission ($p = 0.04$) errors than controls, with medium and small effect sizes, respectively (Table 1). Participants with BD showed a trend-level difference on the number of omission errors ($p = 0.07$) from controls, with a small effect size, but no difference on commission errors ($p = 0.34$). The ADHD and BD groups did not differ on commission ($p = 0.20$) or omission ($p = 0.90$) errors. No effect of group emerged for OXO-not-XOX commission errors ($H_2 = 3.81$, $p = 0.15$).

ERP parameters

Cue condition

An effect of group did not emerge on the Cue-P3 ($F_{2,57} = 1.31$, $p = 0.28$).

A trend-level effect of group emerged for the CNV ($F_{2,57} = 2.86$, $p = 0.07$). *Post-hoc* comparisons showed a significant difference between the ADHD and control groups ($p = 0.05$) and a trend-level difference between the BD and control groups ($p = 0.09$), both with medium effect size (Table 1). No difference emerged between the two clinical groups ($p = 0.85$).

NoGo condition

There was a significant effect of group on the NoGo-N2 ($F_{2,57} = 4.03$, $p = 0.02$). *Post-hoc* analyses revealed that the BD group significantly differed from the ADHD

Table 1. *Cognitive performance and event-related potential measures from the cued continuous performance test: means, effect sizes and significance of group comparisons*

	ADHD ($n = 20$)[a]: mean (S.D.)[b]	BD ($n = 20$): mean (S.D.)[b]	Controls ($n = 20$): mean (S.D.)[b]	ADHD *v.* BD, effect size: *d*	ADHD *v.* controls, effect size: *d*	BD *v.* controls, effect size: *d*
MRT, ms	425.31 (75.74)	418.30 (67.41)	391.58 (63.68)	0.05	0.49[d]	0.44
RTV, ms	109.18 (58.83)	101.73 (37.77)	76.91 (39.24)	0.02	0.60[d]†	0.68[d]*
OE	1.10 (1.55)	1.35 (2.52)	0.60 (1.57)	0.12	0.32*	0.36†
OXO-not-XOX CE	1.05 (1.88)	0.60 (2.04)	0.50 (0.89)	0.23	0.37	0.06
Total CE	7.25 (16.03)	2.40 (5.39)	0.75 (0.97)	0.41	0.57[d]*	0.43
Cue-P3 at Pz	2.30 (1.64)	1.36 (1.80)	1.83 (2.04)	0.56[d]	0.26	0.25
CNV at Cz	−2.24 (1.03)	−2.31 (1.36)	−3.31 (2.12)	0.06	0.66[d]*	0.58[d]†
NoGo-N2 at Fz	0.57 (1.88)	2.41 (2.64)	0.84 (2.07)	0.83[c]*	0.14	0.68[d]*
NoGo-P3 at Cz	5.42 (2.73)	5.56 (3.31)	7.68 (2.57)	0.05	0.88[c]*	0.73[d]*
Go-P3 at CPz	5.01 (2.76)	5.56 (3.23)	6.10 (2.18)	0.19	0.45[d]	0.20

ADHD, Attention-deficit/hyperactivity disorder; S.D., standard deviation; BD, bipolar disorder; MRT, mean reaction time; RTV, within-subject variability in reaction times; OE, omission errors; CE, commission errors; CNV, contingent negative variation.

[a] Only 18 participants with ADHD were included in the average of the Go condition, as two participants did not have at least 20 artefact-free segments.

[b] Means and S.D.s were calculated on raw data.

[c] Large effect size.

[d] Medium effect size.

* $p < 0.05$, † $p < 0.10$.

($p = 0.015$) and control ($p = 0.04$) groups, with large and medium effect sizes, respectively (Table 1). The ADHD and control groups did not differ from each other ($p = 0.66$).

A significant effect of group emerged on the NoGo-P3 ($F_{2,57} = 3.86$, $p = 0.03$). *Post-hoc* analyses showed that both the ADHD ($p = 0.01$) and BD ($p = 0.03$) groups significantly differed from controls, respectively, with large and medium effect sizes (Table 1), but not from each other ($p = 0.88$).

Go condition

No significant effect of group emerged on the Go-P3 ($F_{2,55} = 0.73$, $p = 0.49$).

Discussion

In a direct comparison of women with ADHD, women with BD and control women on cognitive performance and ERP measures from a CPT-OX task, we report evidence for both disorder-specific (conflict monitoring) and overlapping (inhibitory control and potentially response preparation) neurophysiological impairments across the disorders. The current study represents the first cognitive–electrophysiological investigation comparing attentional and inhibitory processing in adults with ADHD and adults with BD. In addition, since the majority of previous ERP studies on ADHD have used male samples (McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013), and very few studies of this kind have been conducted in BD, our all-female sample furthers our understanding of neurophysiological impairments in females with either of these disorders.

Our ERP results show a significant difference between the ADHD and BD groups in the amplitude of the N2 in response to NoGo stimuli, which was reduced in participants with BD compared with the other two groups. The N2 is considered to reflect conflict-monitoring processing (Holroyd *et al.* 2003; Yeung & Cohen, 2006) and to depend on the amount of correct response processing needed to overcome a conflicting response. In the CPT-OX, this process may be represented by the bias towards the response after a cue, which requires the preparation of a response, and produces increased conflict monitoring when the prepared response has to be stopped in presence of a non-target. The reduced N2 in women with BD aligns with previous evidence of attenuated N2 elicited with an oddball task (Ethridge *et al.* 2012) and of a reduced ERN in error responses (Morsel *et al.* 2014). Both N2 and ERN in conditions inducing conflict, such as in non-target or incongruent trials, are thought to reflect

conflict monitoring (Yeung & Cohen, 2006). Our results may therefore indicate that women with BD show impaired conflict monitoring compared with women with ADHD and control women. In line with previous studies using the CPT-OX (McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013), we did not find an attenuated NoGo-N2 in women with ADHD, although reduced N2 have been associated with ADHD in tasks inducing higher conflict demands (McLoughlin *et al.* 2009, 2014*b*).

We also identified abnormalities in ERPs that distinguished women in both clinical groups from controls, indicating shared neurophysiological impairments across ADHD and BD. The reduced P3 in response to NoGo stimuli in both ADHD and BD groups, compared with the control group, suggests a similar pattern of impaired response inhibition to that previously reported in investigations of children and adults with ADHD (McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013). The reduced NoGo-P3 in women with BD also aligns with previous cognitive research finding deficits in inhibitory control in euthymic BD (Robinson *et al.* 2006, 2013). These attenuations of the NoGo-P3 in both disorders therefore probably represent an area of overlapping impairment in brain processes implicated in the inhibition of incorrect response. Yet, this inhibitory control deficit in women with BD was temporally preceded by other processing deficits in the NoGo-N2. As such, in ERPs to non-targets, while women with ADHD seem primarily impaired in response inhibition, women with BD show a broader deficit in both conflict monitoring and inhibitory control.

Additionally, we report an attenuation in the CNV in women with ADHD compared with controls, and also potentially in women with BD (trend-level difference), both with a medium effect size. These results replicate previous studies reporting reduced CNV in individuals with ADHD (McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013; Tye *et al.* 2014), and suggest another potential area of shared impairment with BD. However, we note that the comparison between BD and control participants was only at trend level. If replicated also in BD, this attenuation of the CNV would index an overlapping impairment in response preparation in the two disorders.

The lack of a difference between women with ADHD and controls in the Cue-P3 is inconsistent with some previous investigations showing a reduced Cue-P3 in ADHD samples (McLoughlin *et al.* 2010; Albrecht *et al.* 2013). Yet, these attenuations have not been reported in all studies (Dhar *et al.* 2010; Skirrow, 2012) and the difference in the Cue-P3 emerged as significant, but with a small effect size, in a recent larger-scale study of adolescents and young adults with ADHD (Cheung *et al.* 2015). In the present study, the normal Cue-P3 in ADHD may be due to an effect of gender, the current study being the first using an all-female sample. An age-effect is also plausible, since this study included adults of a slightly older and broader age range compared with previous investigations (e.g. McLoughlin *et al.* 2010) and developmental changes have been reported for the Cue-P3, suggesting that ADHD–control differences may decline with age (Doehnert *et al.* 2013). Further studies on larger samples that include participants of both genders and a broader age range are needed to clarify potential gender and age effects on these processes in ADHD.

While ERP measures of conflict monitoring differentiated the ADHD and BD groups, cognitive performance data did not suggest differences between the two clinical groups. Our cognitive performance results potentially suggest poorer performance and higher RTV in both ADHD and BD groups, compared with controls, consistent with previous studies reporting lower accuracy and higher RTV in ADHD and BD independently (Brotman *et al.* 2009; Kuntsi *et al.* 2010; Torralva *et al.* 2011). This pattern of results, with differences between ADHD and BD groups observed in the neurophysiological markers but not at the cognitive performance level, may reflect greater specificity of the neurophysiological markers in detecting differences between clinical groups.

The following limitations of this study should be taken into account when interpreting these data. First, although the groups were matched on gender, age and IQ, there were differences in the prescribed medications that participants with ADHD or BD were taking. While we asked participants with ADHD to stop taking stimulant medications 48 h prior to the assessment, it was not possible, for ethical reasons, to ask participants to stop mood-stabilizing, anti-psychotic or antidepressant medications. Given limited numbers in medication subgroups, we were not able to directly test the effect of medication on ERP measures, which represents a limitation of the current study. The effects of medication are difficult to control for in cross-disorder comparison studies where different treatments may be prescribed to different groups of psychiatric patients. Although the understanding of the effects of medications on ERPs is still limited, previous studies suggest that medications may normalize ERP measures (Anderer *et al.* 2002; Karaaslan *et al.* 2003; Galletly *et al.* 2005). As such, in this study, a medication effect could potentially have resulted in ERPs comparable with controls. Yet, both clinical groups, although some participants were medicated, showed reduced ERP measures compared with controls. Therefore, although the effect of medication

represents a potential confounder of this study and may have attenuated some case–control differences, we report impairments in both clinical groups which may not have been produced by the effect of medication. Future studies on samples including non-medicated individuals or a higher number of individuals in each medication subgroup are needed to clarify whether our results may have been affected by medication effects. A second limitation is that, by using an area measure, we were not able to obtain latency data. This approach, previously adopted in similar ERP studies (Groom *et al.* 2010; Tye *et al.* 2014), was preferred for having the advantage, over peak measures, of being unaffected by latency variability and of providing a reliable measure of amplitude even when the identification of clear peaks is not possible for all subjects (Luck, 2005). Although some previous studies found prolonged latency of ERP components in BD (Chun *et al.* 2013; Maekawa *et al.* 2013), our ERP grand averages did not suggest latency differences, thus our area measure probably captured most of the differences between the groups on ERP measures. Finally, in order to increase homogeneity of the sample, this investigation was conducted on an all-female sample, with slightly higher than expected IQ in the clinical groups. Replication in future investigations with bigger samples of both genders and including individuals with a wider range of IQs is required in order to generalize these findings to more typical clinical populations.

Conclusion

In conclusion, our results represent some of the first evidence of disorder-specific and shared impairments in brain processes involved in attentional orienting, conflict monitoring and inhibitory control in women with ADHD and BD, with moderate to large effect sizes. This investigation of neurophysiological processes furthers our understanding of impairments associated with ADHD and BD, and the identification of objective measures showing differences between ADHD and BD may assist in differentiating between the two disorders when their distinction is not clear at clinical consultations. If replicated in larger-scale studies, the neurophysiological biomarkers of distinct patterns in brain activity may aid in the identification of the diagnostic boundaries of ADHD and BD in adults. More broadly, given that ADHD and BD are both highly heritable disorders, the identified neurophysiological indices may represent intermediate phenotypes between diagnosis and genetic factors influencing a disorder, as suggested by genetic and family studies on ERP indices of attentional and inhibitory processing showing shared familial/genetic influences with ADHD (McLoughlin *et al.* 2011; Albrecht *et al.* 2013, 2014). Future studies can investigate causal models of ADHD and BD, by exploring to what extent overlapping and disorder-specific impairments in brain function are accounted for by specific or shared genetic influences on the two disorders and, in turn, further our understanding on the pathways to distinct and overlapping features in ADHD and BD.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715001877

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Declaration of Interest

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Note

[1] Since most previous ERP analyses on CPT-OX did not apply a baseline subtraction (Banaschewski *et al.* 2004; McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013), analyses were also repeated without baseline correction. Results of data without baseline

correction were comparable for the NoGo-N2, NoGo-P3 and Go-P3, but partly changed for the Cue-P3 and CNV (see Supplementary material).

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CHAPTER 6 - Shared and disorder-specific event-related brain oscillatory markers of attentional dysfunction in ADHD and bipolar disorder

6.1 Abstract

Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) often present with overlapping symptoms and cognitive impairments, such as increased fluctuations in attentional performance measured by increased reaction time variability (RTV). In a direct electrophysiological comparison, we previously provided initial evidence of shared and distinct event-related potential (ERP) impairments in ADHD and BD, but the overlapping or specific neural mechanisms underlying attentional impairments in these disorders remain to be understood. Here, we aimed to further identify and compare the neural underpinnings of impaired attentional processes in ADHD and BD by examining event-related brain oscillations during a reaction time task under slow-unrewarded baseline and fast-incentive conditions. We measured cognitive performance, ERPs and brain-oscillatory modulations of power and phase variability in 20 women with ADHD, 20 women with BD (currently euthymic) and 20 control women. Compared to controls, both ADHD and BD groups showed increased RTV in the baseline condition and increased RTV, theta phase variability and lower contingent negative variation (CNV) in the fast-incentive condition. Unlike controls, neither clinical group showed an improvement from baseline to fast-incentive condition in attentional P3 amplitude or alpha power suppression. Most impairments did not differ between the disorders, as only an adjustment in beta suppression between conditions (lower in the ADHD group) distinguished between the clinical groups. These findings suggest shared impairments in women with ADHD and BD in cognitive and neural variability, preparatory brain activity and inability to adjust neural attention allocation and activation. The overlapping impairments in neural markers may represent shared neurobiological mechanisms of attentional dysfunction in ADHD and BD, and may underlie common symptoms in both disorders.

6.2 Introduction

The abilities to regulate alertness and sustain attention are essential for efficient information processing and behaviour (Posner and Petersen, 1990). Such cognitive processes are traditionally measured with reaction time variability (RTV), capturing the consistency and short-term fluctuations in response speed during attentional performance in cognitive tasks (Kuntsi et al., 2013, Ode et al., 2011). Increases in RTV are characteristic of several psychiatric disorders (Kaiser et al., 2008), including attention-deficit/hyperactivity disorder (ADHD) (Kofler et al., 2013, Wood et al., 2010) and bipolar disorder (BD) (Brotman et al., 2009, Moss et al., 2016). ADHD and BD are common psychiatric conditions in adults (Merikangas et al., 2011, Willcutt, 2012), which severely impact many aspects of individuals' lives (Skirrow et al., 2012, Asherson et al., 2014). Although ADHD and BD represent distinct disorders, they present with common symptoms of distractibility and difficulty concentrating, which can lead to uncertainty regarding the boundaries of the two disorders (Asherson et al., 2014, Kitsune et al., 2016). These overlapping symptoms may reflect, at the cognitive level, the common fluctuations in attentional performance and increased RTV displayed by individuals with ADHD and BD (Kuntsi et al., 2014, Albaugh et al., 2017). Increased RTV is also observed in unaffected first-degree relatives of individuals with either disorder, compared to individuals without family risk, representing a candidate marker of genetic/familial risk for both disorders (Adleman et al., 2014, Thissen et al., 2014, Andreou et al., 2007). Direct comparisons of impairments in attentional performance between ADHD and BD may lead to new insights into the pathways to overlapping symptoms and cognitive dysfunction in both disorders. Yet, cross-disorder comparisons in ADHD and BD are limited to date (Michelini et al., 2016b, Torralva et al., 2011, Rommel et al., 2016).

Previous research on RTV in psychiatric disorders has addressed the question of whether dysfunctions in alertness and attentional performance, rather than being stable, could be malleable and sensitive to context changes, such as task manipulations. RTV impairments in children and adolescents with ADHD are maximal in slow and unrewarded conditions, but with the introduction of faster event rate and incentives may improve significantly more than in neurotypical individuals (Andreou et al., 2007, Kuntsi et al., 2013, Cheung et al., 2017, Slusarek et al., 2001, Uebel et al., 2010). It remains unknown, however, whether RTV also improves in adults with ADHD. Initial evidence also indicates potential malleability of RTV in BD, as suggested by one study showing increased RTV in individuals with BD in a continuous performance task (CPT) with low target frequency, but not with high target frequency (Moss et al., 2016). The evidence of malleability in RTV is clinically relevant, as it may point to room for improvement in

the observed cognitive impairment, which could be targeted in new interventions for the disorders, aimed at reaching and maintaining an optimal state of alertness (Cheung et al., 2017, Kuntsi and Klein, 2012). Understanding whether the same or different mechanisms underlie attentional fluctuations and their potential reduction in individuals with ADHD and BD may thus potentially inform the development of interventions for ADHD and BD. No study to date, however, has compared adults with ADHD and adults with BD on the malleability of attentional fluctuation indexed by RTV.

The investigation of brain responses using the millisecond temporal precision of electroencephalography (EEG) can help elucidate the neural correlates of a suboptimal attentional performance. Most EEG studies on attentional impairments in ADHD or BD samples have employed event-related potentials (ERPs), measuring transient enhancements in brain activity following an event (Luck, 2014). ERP studies in adults with ADHD have shown attenuated contingent negative variation (CNV) components over central regions (reflecting atypical response anticipation and preparation) (McLoughlin et al., 2010, Michelini et al., 2016b, Valko et al., 2009) and reduced attentional P3 components over parietal regions (reflecting impaired attentional resource allocation) (Cheung et al., 2017, Cheung et al., 2016, McLoughlin et al., 2010, Szuromi et al., 2011). Similarly, impairments in P3 and CNV in BP during attentional tasks have also been found (Maekawa et al., 2013, Fridberg et al., 2009, Li et al., 2015). Yet, only a few direct comparisons have examined whether cognitive and ERP indices are affected to a similar extent in ADHD and BD. In a recent investigation using a cued CPT paradigm, we showed that increased RTV and reduced CNV may represent shared attentional impairments in ADHD and BD (Michelini et al., 2016b). Using quantitative EEG (QEEG), we further reported that both ADHD and BD groups showed higher spontaneous EEG theta power during rest and a lack of a task-related increase in theta from rest to CPT task compared to controls (Rommel et al., 2016). These results indicate potentially shared impairments in attentional processes in both disorders. Yet, in ERP analyses, the attentional P3 components in response to Cue and Go stimuli were intact in both groups, consistent with other studies that also failed to report P3 reductions in adults with ADHD (Dhar et al., 2010, Michelini et al., 2016b, Grane et al., 2016) or BD (Bestelmeyer, 2012, Chun et al., 2013, Michelini et al., 2016b). One possible reason for inconsistencies between studies using different attentional paradigms is that the attentional P3, similar to RTV, may reflect a context-dependent and potentially malleable, rather than stable, impairment (Cheung et al., 2017). We recently reported that a reduced parietal P3 in a slow and unrewarded condition in adolescents and young adults with ADHD improved with faster event rate and rewards significantly more than in neurotypical controls (Cheung et al., 2017). In contrast, for

CNV, the ADHD group showed reduced amplitude compared to controls only in the fast and rewarded condition. No study has examined the malleability of these ERPs with faster rate and incentives in BD. Further direct comparisons between ADHD and BD are needed to clarify what neurophysiological impairments overlap between the two disorders, and whether ADHD and BD may show similar malleability with a changed context.

Advances in EEG methods called time-frequency analyses, combining the strengths of ERP and QEEG methods, further allow to capture event-related brain oscillatory dynamics, which reflect sub-second modulations of power and phase in response to an event across the full EEG spectrum (Loo et al., 2015, Pfurtscheller and Lopes da Silva, 1999, Makeig et al., 2004a, Klimesch, 1999). Processing and focusing attention on a relevant stimulus have been associated with various event-related brain oscillatory phenomena in the time-frequency domain not captured by ERP or QEEG approaches: (1) an event-related synchronisation (ERS) or increase in theta (3-7 Hz) power over fronto-central (Bickel et al., 2012, Mazaheri et al., 2014, Lenartowicz et al., 2014) or parietal (Babiloni et al., 2004, Jacobs et al., 2006) regions, reflecting the initial processing of the stimulus; (2) an event-related desynchronisation (ERD) or suppression of power in posterior alpha (8-13 Hz), reflecting attentional selection and cortical activation (Klimesch, 2012, Mazaheri and Picton, 2005); and (3) an ERD in central beta (14-30 Hz) when a motor response is required (Pfurtscheller, 1981, Guntekin et al., 2013). Additionally, indices of consistency of the phase (i.e., the "timing") of brain oscillations over trials can reveal whether the processing of a stimulus repeated over time reflects stable or variable neural mechanisms (Makeig et al., 2004a, Papenberg et al., 2013, Klimesch, 2012). Greater alpha and beta ERD and theta phase consistency have further been associated with better task performance (McLoughlin et al., 2014b, Klimesch, 2012, Bickel et al., 2012). Multiple brain-oscillatory correlates of attentional processes may be affected in ADHD and BD. Individuals with ADHD have been reported to show reductions in event-related phase consistency in the theta band (McLoughlin et al., 2014b, Groom et al., 2010a), alpha ERD (Lenartowicz et al., 2014, ter Huurne et al., 2013), and beta ERD (Hasler et al., 2016). Emerging evidence also suggests that individuals with BD show attenuations in event-related theta (Atagun et al., 2013, Ethridge et al., 2012) and alpha power (Ethridge et al., 2012, Basar et al., 2012) and increases in beta power (Ozerdema et al., 2013, Tan et al., 2016). These studies in BD, however, applied time-frequency analyses on averaged ERP responses, thus not allowing the characterisation of both ERD and ERS dynamics (Bickel et al., 2012). The investigation of fine-grained brain-oscillatory indices underlying attentional processes with time-frequency analyses may allow a deeper investigation into the neural correlates of attentional performance, and help identify distinct or comparable

impairments in neural processes between the two disorders (Loo et al., 2015). However, no study to date has compared ADHD and BD on time-frequency indices of brain oscillations, or whether these indices, like RTV, show adjustments under context changes, such as fast and rewarded conditions.

The present study aims to investigate and compare cognitive-performance, ERP and detailed event-related power modulations of theta, alpha and beta oscillations and of phase variability in theta oscillations, previously linked to attentional processes, in adults with ADHD and adults with BD. We used an all-female sample, to match the groups on sex but also because little is known on these processes in females, especially in relation to ADHD (McLoughlin et al., 2010, Saville et al., 2015). Participants completed the same four-choice RT task used in our previous studies of ADHD (Kuntsi et al., 2006, Andreou et al., 2007, Cheung et al., 2017), which compares a slow-unrewarded baseline condition with a fast-incentive condition designed to specifically reward reduction of RTV. A further aim is to examine whether differences in adjustments in the investigated cognitive-performance, ERP and brain-oscillatory indices with a faster event rate and incentives emerge between groups, which could inform the development of cognitive/brain training programs for ADHD and BD.

6.3 Methods

6.3.1 Sample

The sample consisted of 20 women with ADHD, 20 with BD and 20 control women, aged between 20-52 years (Table 6.1). Participants with ADHD were recruited from the National Adult ADHD Clinic at the Maudsley Hospital, where any female cases meeting inclusion criteria were considered for potential inclusion in the study. Participants with BD were recruited from the Maudsley Psychosis Clinic and a sample that had previously participated in another research study (Hosang et al., 2012). Control participants were recruited from the Mindsearch volunteer database maintained by the Institute of Psychiatry, Psychology and Neuroscience, King's College London, which comprises several thousand potential participants. Participants were randomly selected from all those meeting recruitment criteria for this study.

Diagnosis in the clinical groups was confirmed by checking medical records for details of diagnosis and psychiatric history, following DSM-IV criteria. Participants in the ADHD group had

a current combined-type diagnosis or an inattentive-type diagnosis with sufficient symptoms of hyperactivity-impulsivity in childhood to meet a childhood combined-type diagnosis. Participants in the BD group had a diagnosis of BD Type I, having experienced at least one manic episode in the past. Those who were experiencing a manic episode at the time of the assessment were excluded; all participants included in the BD group were currently euthymic. Exclusion criteria for all groups were drug or alcohol dependency in the last 6 months, autism, epilepsy, neurological disorders, brain injury, past ECT treatment, current involvement in another research trial likely to alter symptom severity, pregnancy or a limited proficiency in English language. Individuals with ADHD and individuals with BD with a reported comorbidity of both ADHD and BD were also excluded. Control participants, who reported a history of psychiatric disorders or who were taking psychiatric medication, were excluded from the study. Comorbidity in the clinical groups and lack of psychiatric disorders in the control group were further assessed through clinical evaluations when participants underwent the cognitive-EEG assessment for this study. Further details on the clinical assessment of this sample can be found elsewhere (Kitsune et al., 2016). In brief, ADHD was excluded in the BD group after conducting the Diagnostic Interview for Adult ADHD (DIVA v. 2.0; Ramos-Quiroga et al., 2016). BD was excluded in the ADHD group by checking for a history of past episodes of depression or hypomania/mania and evaluating current mood symptoms using the Altman Self-Rating Mania Scale (Altman et al., 1997) and the Beck Depression Inventory (Beck et al., 1996), and current and lifetime ever symptoms using the Young Mania Rating Scale (Young et al., 1978). The ADHD and BD groups did not differ significantly on any of the mood scales for current symptoms (Kitsune et al., 2016).

Table 6.1. Sample demographics divided by group, with ANOVA test for group differences

	ADHD Mean (SD)	BD Mean (SD)	Ctrl Mean (SD)	F	p
Age	37.4 (7.7)	40.3 (7.7)	36.7 (4.3)	1.63	0.21
IQ	104 (17.9)	108 (12.5)	112 (14.2)	1.37	0.26

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; Ctrl, control group; F, ANOVA statistic; p, p value from the ANOVA.
Note: group differences on age and IQ were tested with univariate ANOVAs.

6.3.2 Procedure

Participants attended a single 4.5-hour research session (including breaks) for cognitive-EEG assessment, IQ assessment and clinical interviews. An estimate of IQ was derived with the Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV; Wechsler, 1999). All participants were asked to refrain from caffeinated drinks and nicotine two hours before assessments. Participants with ADHD were asked to stop taking any stimulant medication prescribed for their ADHD 48 hours prior to the assessment. For ethical reasons, participants were not asked to stop taking mood stabilisers (70% of the BD group), anti-psychotic medication (40% of the BD group) or anti-depressants (7% of the ADHD group and 25% of the BD group) they had been prescribed. Ethical approval for the study was granted by the Camberwell St Giles Research Ethics Committee (approval number 11/LO/0438) and all participants provided informed consent.

6.3.3 Fast task

The task for this analysis was a computerised four-choice RT task which measures performances under a slow-unrewarded and a fast-incentive condition (Andreou et al., 2007, Kuntsi et al., 2006). In both conditions speed and accuracy were emphasised equally. The baseline (slow-unrewarded) condition followed a standard warned four-choice RT task (Figure S6.1, Appendix E). A warning signal (four empty circles, arranged side by side) first appeared on the screen. At the end of the fore-period lasting 8 s (presentation interval for the warning signal), the circle designated as the target signal for that trial was filled (coloured) in. The participant was asked to make a compatible choice by pressing the response key that directly corresponded in position to the location of the target stimulus. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. If the participant did not respond within 10 s, the trial terminated. First, a practice session was administered, during which the participant had to respond correctly to five consecutive trials. The baseline condition, consisting of 72 trials, then followed.

To investigate the extent to which a response style characterised by slow and variable speed of responding may be reduced, the task includes a comparison condition that uses a fast event rate (fore-period of 1 s) and incentives (Figure S6.1, Appendix E). This condition started immediately after the baseline condition and consisted of 80 trials, with a fixed inter-trial interval of 2.5 s following the response. The participants were told to respond as quickly as possible to each

target, in order to win smiley faces and earn real prizes at the end. Participants won a smiley face for responding faster than their own mean reaction time (MRT) during the baseline (first) condition consecutively for three trials. The baseline MRT was calculated here based on the middle 94% of responses (the exclusion of the top and bottom 3% of responses is only used when calculating a baseline MRT for the set-up of the fast-incentive condition, and is not used for analyses), therefore excluding extremely fast and extremely slow responses. The smiley faces appeared below the circles in the middle of the screen and were updated continuously. The fast-incentive condition was always administered after the baseline condition and, as such, did not involve a similar learning phase. Participants earned £5 in cash after the task battery. RTV for correct responses in each condition was measured to assess task performance.

6.3.4 EEG recording and pre-processing

The EEG was recorded from a 62-channel DC-coupled recording system (extended 10-20 montage) (Brain Products, Gilching, Germany), using a 500 Hz sampling-rate, impedances under 10 kΩ, and FCz as the recording reference. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. EEG recordings were pre-processed and analysed using the EEGLAB toolbox (Delorme and Makeig, 2004) in Matlab (MathWorks, Natick, MA, USA). Researchers were blind to group status during EEG pre-processing and analysis. Raw EEG recording were down-sampled to 256 Hz, re-referenced to the average of all electrodes (turning FCz into an active channel), and digitally filtered using a 0.25 Hz (-6 dB cut-off) high-pass filter and a 35 Hz (-6 dB cut-off) low-pass filter. Independent component analysis (ICA) (Jung et al., 2000) was used to identify and remove ocular (blink-related and vertical and horizontal eye movements) and muscular artefacts. Visual inspection was carried out for all trials to manually remove further artefacts. Channels showing technical problems or excessive electrical noise were removed and replaced with topographic spline interpolation after ICA, to estimate a virtual EEG activity based on artefact-free activity from other channels.

6.3.5 ERP and time-frequency analyses

Only participants with at least 20 artefact-free EEG segments in each condition were included in ERP/EEG analyses. All ERP/EEG analyses were performed using EEGLAB functions (Delorme and Makeig, 2004) and Matlab custom scripts. ERPs were identified within the selected electrodes and latency windows for which effects were expected to be maximal, based on our previous ERP

analyses of this task (Cheung et al., 2017, James et al., 2017) and verified against the topographic maps and the grand averages (Figure 6.1, Figure S6.2, Appendix E). Following our previous work (Cheung et al., 2017), P3 amplitudes were analysed at Pz between 300 and 550 ms (Figure S6.2, Appendix E) following the target as the area amplitude measure (μV*ms), to reduce bias due to the varying noise levels induced by the different task conditions (Luck, 2014). All trials were baseline-corrected by subtracting the mean activity (200 ms before target onset) from the P3 ERPs. The mean amplitudes of this pre-target period between -200 and 0 ms were also analysed separately as a CNV measure at Cz (Figure 6.1) with technical zero-baseline approach (which measures the absolute state rather than the amount of neural change introduced by the event) following previous CNV work (Albrecht et al., 2013, Banaschewski et al., 2003, Cheung et al., 2017). This short CNV interval, characterised by a typical CNV topography in the fast-incentive condition with its 1000 ms warning-target interval, was chosen as it captures the late CNV component unconfounded by the processing of warning stimuli. Although no typical CNV emerged in the slower baseline condition, CNV amplitude at Cz in the same corresponding time window was used to examine within-subject change in preparatory activity across conditions.

Time-frequency analyses examined the target-related modulations of power and phase consistency of brain oscillations previously implicated in attentional processes. Modulations of power were quantified with the event-related spectral perturbation (ERSP) index (Delorme and Makeig, 2004). ERSP values were computed in a 4000 ms window (from -2000 to 2000 ms) centred around target onset by applying a Morlet wavelet decomposition of frequencies between 3-30 Hz, with linearly increasing number of cycles (frequency step of 0.80 Hz) from 2 cycles for the lowest frequency (3 Hz) to 24.60 cycles for the highest frequency (30 Hz). Each ERSP trial was normalised with respect to the mean log-power spectrum from the pre-stimulus period, from -2000 to -1000 ms, corresponding to the 1000 ms preceding the warning onset in the fast-incentive condition; the same comparable window was used in the baseline condition as the long fore-period before targets did not produce a modulation of power before stimulus onset in the baseline condition (see Appendix E for further explanation). Averaging all ERSPs across trials produced a time-frequency representation in decibel (dB) units of increases (ERS, in red) and decrease (ERD, in blue) in the spectral power at a given frequency and latency with respects to pre-stimulus activity (Figures 6.2-6.3), from which frequency-specific ERSPs can be extracted. Phase consistency was calculated with the inter-trial phase coherence (ITC) index, measuring the degree to which the phase of the evoked response (derived from the same Morlet wavelet used for the ERSP index) at a given latency and frequency is consistent across trials (Tallon-Baudry et al., 1996, Makeig et al., 2004a, Delorme and Makeig, 2004). ITC values are

independent of power, and range from 0 (reflecting absence of phase consistency and highest phase variability across trials) to 1 (indicating perfect phase consistency and lowest phase variability) (Figure 6.4).

Target-related ERSP in the theta (3-7 Hz), alpha (8-13 Hz) and beta (14-30 Hz) bands were extracted in the 1000 ms window capturing the broad target-related modulation of power, divided into two consecutive windows for earlier (0-500 ms) and later (500-1000 ms) processing (Figures 6.2-6.3, Figure S6.3, Appendix E). ITC was measured at target onset in the first window (0-500 ms), where greater phase consistency in response to the event was observed (Figure 6.4), as expected (Groom et al., 2010a). The ITC analysis was restricted to the theta band, consistent with previous studies reporting a role of this frequency band in neural consistency (Groom et al., 2010a, McLoughlin et al., 2014b, Papenberg et al., 2013). ERSP and ITC were measured at scalp locations where they were maximal (Figures 6.2-6.4, Figure S6.3, Appendix E), in line with previous studies on similar attentional processes: theta over parietal regions (average of electrodes: CPz, CP1-CP6, Pz, P3-P4) (Jacobs et al., 2006, DeLosAngeles et al., 2016); alpha over parieto-occipital regions (average of electrodes: Pz, P3-P4, P7-P8, POz, PO3-PO4, PO7-PO8) (Bickel et al., 2012, Mazaheri and Picton, 2005); beta over central regions (average of electrodes: Cz, C1-C4, CPz, CP1-CP4) (Bickel et al., 2012, Mazaheri and Picton, 2005).

6.3.6 Statistical analyses

All measures were investigated using random intercept linear models (i.e., multilevel regression models). Main effects of group (ADHD vs BD vs control), condition (baseline vs fast-incentive) and group-by-condition interactions were examined. Significant ($p<0.05$) and trend-level ($p<0.09$) effects were followed up with post-hoc analyses testing for (1) between-group differences in baseline and fast-incentive conditions separately, and (2) within- and between-group effects of change between conditions with difference scores. Since ERSP indices were measures at two time windows (0-500 ms, 500-1000 ms), we tested for three-way group-by-condition-by-time interactions for these measures, followed by additional post-hoc tests examining group differences in each time window. Since groups did not differ on IQ or age (Table 6.1), these variables were not controlled for in analyses. Measures that showed skewed distributions were transformed to normal with square root (CNV, P3) and with logarithm using the "lnskew0" Stata command (MRT, RTV, beta ERSP). For between-group comparisons, we report both p-values and Cohen's d effect sizes, calculated using the difference in the means divided by the pooled standard deviation, where $d \geq 0.20$ constitutes a small effect, $d \geq 0.50$ a

medium effect and d≥0.80 a large effect (Cohen, 1988). All statistical analyses were run in Stata 14 (Stata Corp, College Station, TX, USA). Data on the fast-incentive condition were missing for one participant with ADHD due to technical issues during the testing session. Two control participants had outlier RTV (>5 SD) in the baseline condition, indicating that they did not follow task instructions, and were excluded from all analyses. As at least 20 artefact-free EEG segments are needed to obtain reliable ERP/EEG indices (McLoughlin et al., 2009), one participant with ADHD and one with BD were excluded from ERP/EEG analyses on the baseline condition, and one control from ERP/EEG analyses on both conditions. Due to the longer fore-period in the baseline condition, the two conditions were matched on the number of trials, but not on length. To control for this, we run the analyses of RTV performance first on the full baseline condition, and separately on a length-matched segment of the baseline (Andreou et al., 2007) (Appendix E). Condition length was not controlled for in the ERP/EEG analyses, as data from the full baseline condition was required to obtain sufficient (>20) trials for averaging.

6.4 Results

6.4.1 RTV

Significant group (p=0.01) and condition (p<0.001) effects, but no group-by-condition interaction (p=0.92), emerged for RTV. Post-hoc tests of group effects showed that the ADHD and the BD groups had significantly increased RTV compared to controls in both conditions, but did not differ significantly from one another (Table 6.2). Post-hoc analyses of condition effects showed that all three groups had a significant within-group decrease in RTV from the baseline to the fast-incentive condition, with no significant differences between groups in the degree of change between conditions (Table 6.3). Comparable results were obtained using the length-matched segment of the baseline condition (Appendix E).

6.4.2 ERPs

CNV. Significant main effects of group (p=0.03) and condition (p<0.001), and a significant group-by-condition interaction (p<0.01), emerged for the CNV. Post-hoc tests showed no group differences in the baseline condition (Table 6.2). In the fast-incentive condition, the CNV was significantly reduced in the ADHD compared to the control group (Figure 6.1). The BD group showed significantly reduced CNV compared to controls, and a trend-level effect for greater CNV compared to the ADHD group (Table 6.2). All three groups had a significant within-group

decrease from the baseline to the fast-incentive condition (Table 6.3, Figure 6.1). The degree of change in CNV between conditions in the ADHD group was significantly lower compared to the control group, and at trend level compared to the BD group. The BD group also showed a trend-level reduction in CNV compared to the control group in the degree of change between conditions.

P3. A trend-level group-by-condition interaction (p=0.06), but no main effects of group (p=0.84) or condition (p=0.56), emerged for the P3. Post-hoc tests did not show significant group differences in the baseline or in the fast-incentive condition (Table 6.2, Figure S6.2, Appendix E). A significant within-group change from the baseline to the fast-incentive condition in stimulus-locked P3 emerged in controls, but not in participants with ADHD or BD (Table 6.3). The degree of change between conditions was significantly lower in the BD compared to the control group. The ADHD group did not differ significantly from the other two groups in the degree of change between conditions.

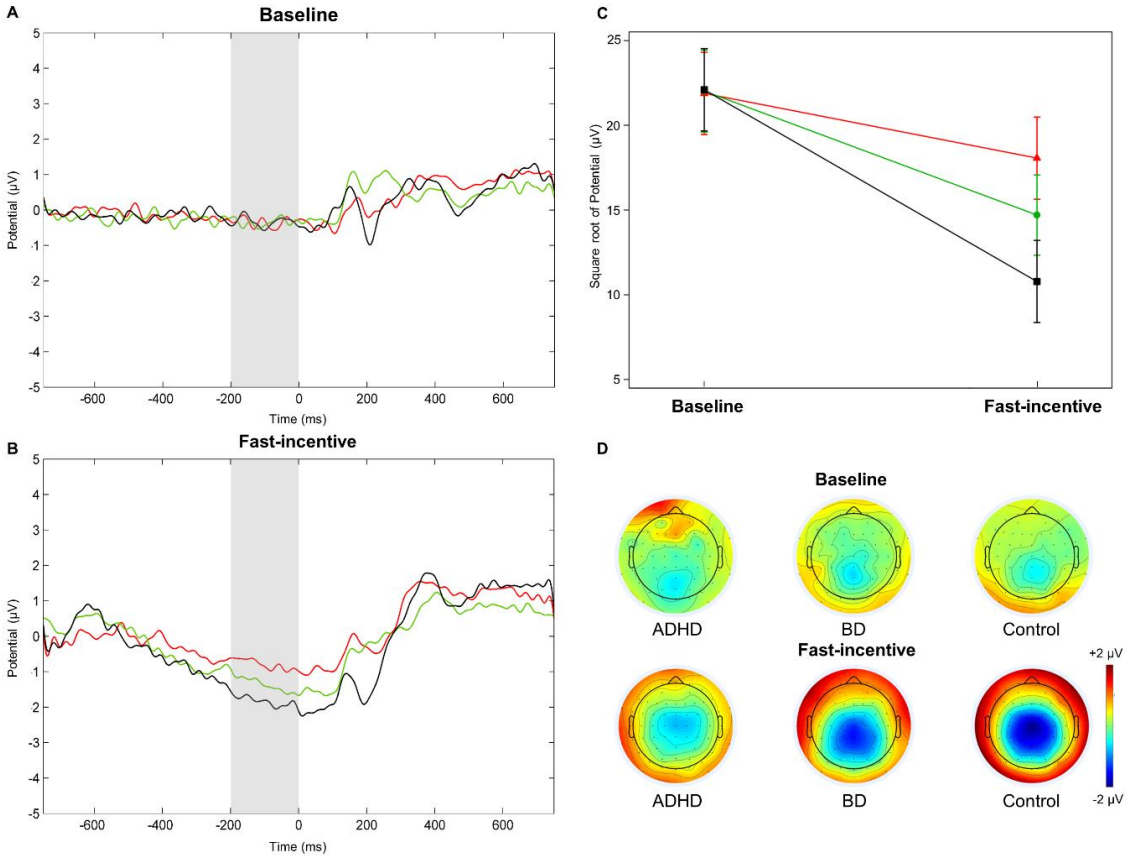

Figure 6.1. *Contingent negative variation (CNV) amplitude measured at Cz in the -200–0 ms window in the ADHD (in red), BD (in green) and control (in black) groups across the baseline and*

fast-incentive conditions of the Fast task. (A) Grand average in the baseline condition; (B) Grand average in the fast-incentive condition; (C) Condition effects by group; (D) Topographic maps by group at each condition.

6.4.3 Event-related power (ERSP)

Theta. No effects of group (p=0.96), condition (p=0.11) or group-by-condition-by-time interaction (p=0.94) emerged for theta ERSP. After removing the three-way interaction, there were no significant group or group-by-condition interaction effects on this measure (p>0.61), and a significant main effect of condition emerged in the 0-500 ms window (p<0.001) but not in the 500-1000 ms window (p=0.41). In the 0-500 ms window, a significant within-group decrease from the baseline to the fast-incentive condition emerged in theta ERSP for the ADHD and BD groups, and at trend level for the control group (Table 6.3), but there were no group differences in the degree of change between conditions (Table 6.3). An additional analysis examined the event-related theta ERSP that was evident also at fronto-central regions (Figure S6.3, Appendix E), yielding the same results as found for parietal theta power (Tables 6.2-6.3).

Alpha. A main effect of condition (p<0.001), but no effects of group (p=0.25) or group-by-condition-by-time interaction (p=0.23), emerged for alpha ERSP. After removing the three-way interaction, there was a significant effect of condition (p<0.001), but no significant group (p=0.30) or group-by-condition interaction effects in the 0-500 ms time window for this measure (p=0.48). All three groups showed a significant within-group decrease in alpha ERSP (i.e., increase in alpha suppression) in the change from the baseline to the fast-incentive condition (Table 6.3), but there were no group differences in the degree of change between conditions. In the 500-1000 ms window, a main effect of condition (p=0.01), a trend-level group-by-condition interaction (p=0.08), but no main effect of group (p=0.23), emerged for alpha ERSP. Post-hoc tests showed no differences between groups in the baseline condition (Table 6.2). In the fast-incentive condition, the ADHD group showed a significantly decreased alpha ERSP (i.e., lower alpha suppression) compared to controls (Figure 6.3). The BD group did not differ from the other groups. A significant within-group decrease from the baseline to the fast-incentive condition in alpha ERSP (i.e., increase in alpha suppression) emerged for the control group, but not for the ADHD or BD groups (Table 6.3). The ADHD group showed a significantly lower degree of change between conditions than the control group in this measure, while the BD group did not differ from the other groups (Table 6.3).

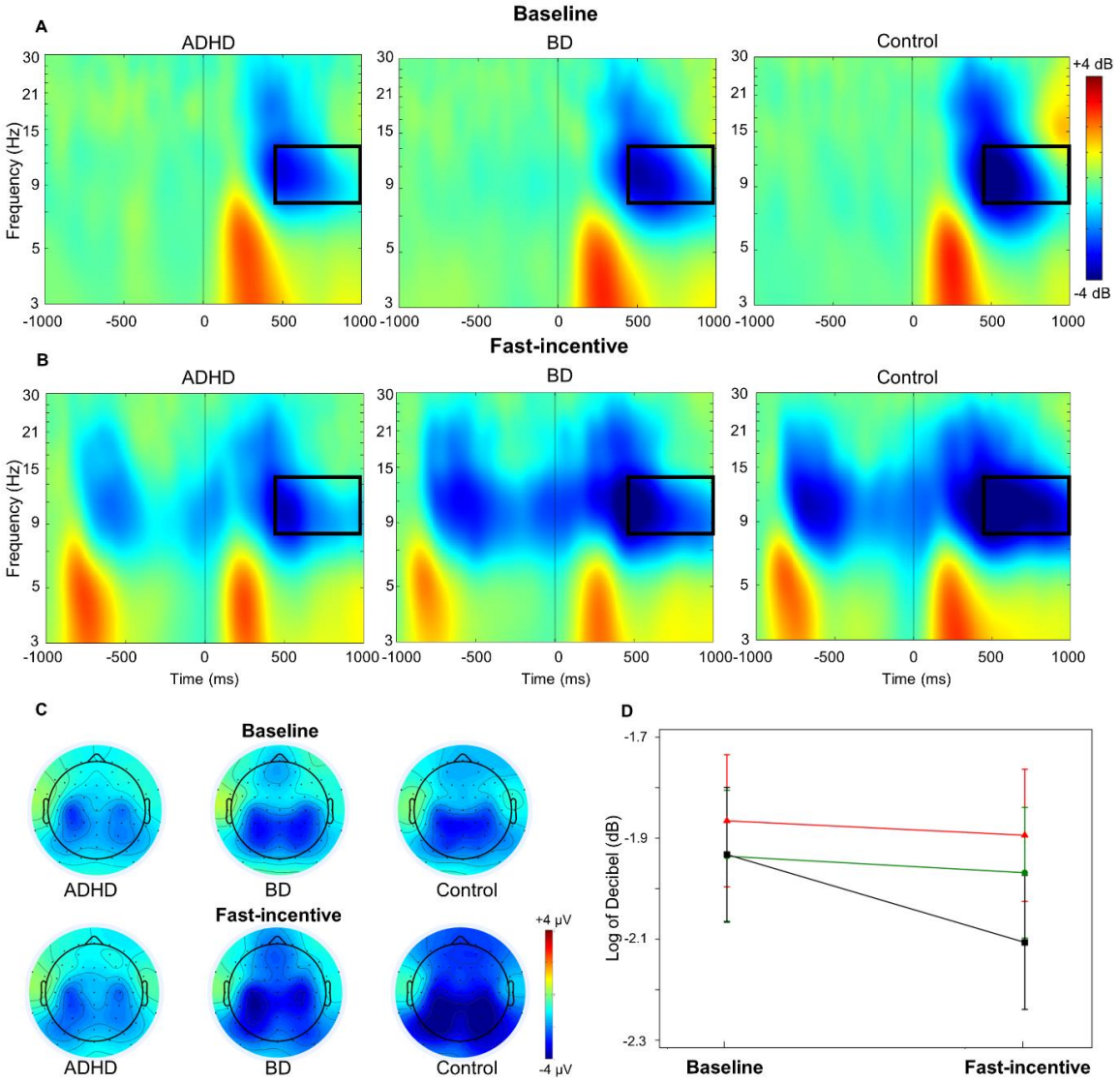

Figure 6.2. *Alpha event-related spectral perturbation (ERSP) at parieto-occipital regions in the ADHD, BD and control groups in the baseline and fast-incentive conditions of the Fast task. (A) ERSP in the baseline condition; (B) ERSP in the fast-incentive condition; (C) Topographic maps by group in the 500-1000 ms window at each condition; (D) Condition effects in the 500-1000 ms window by group (ADHD group in red, BD group in green, control group in black).*

Beta. A significant main effect of condition ($p<0.001$), but no significant effect of group ($p=0.75$) or group-by-condition-by-time interaction ($p=0.61$), emerged for beta ERSP. After removing the three-way interaction, there was no significant group effects in either time window ($p>0.25$), but there were significant condition ($p<0.001$) and trend-level group-by-condition interaction ($p=0.06$) effects in the in the 0-500 ms window, and significant group-by-condition interaction ($p=0.01$) and trend-level condition ($p=0.08$) effects in the 500-1000 ms window. A significant within-group decrease in beta ERSP (i.e., increase in beta suppression) from the baseline to the fast-incentive condition emerged for all groups in the 0-500 ms window, but only for control and BD groups in the 500-1000 ms window (Table 6.3, Figure 6.3). The ADHD group differed from the BD and control groups in the degree of change in beta ERSP between conditions in both time windows, while the BD and control groups did not differ from one another (Table 6.3).

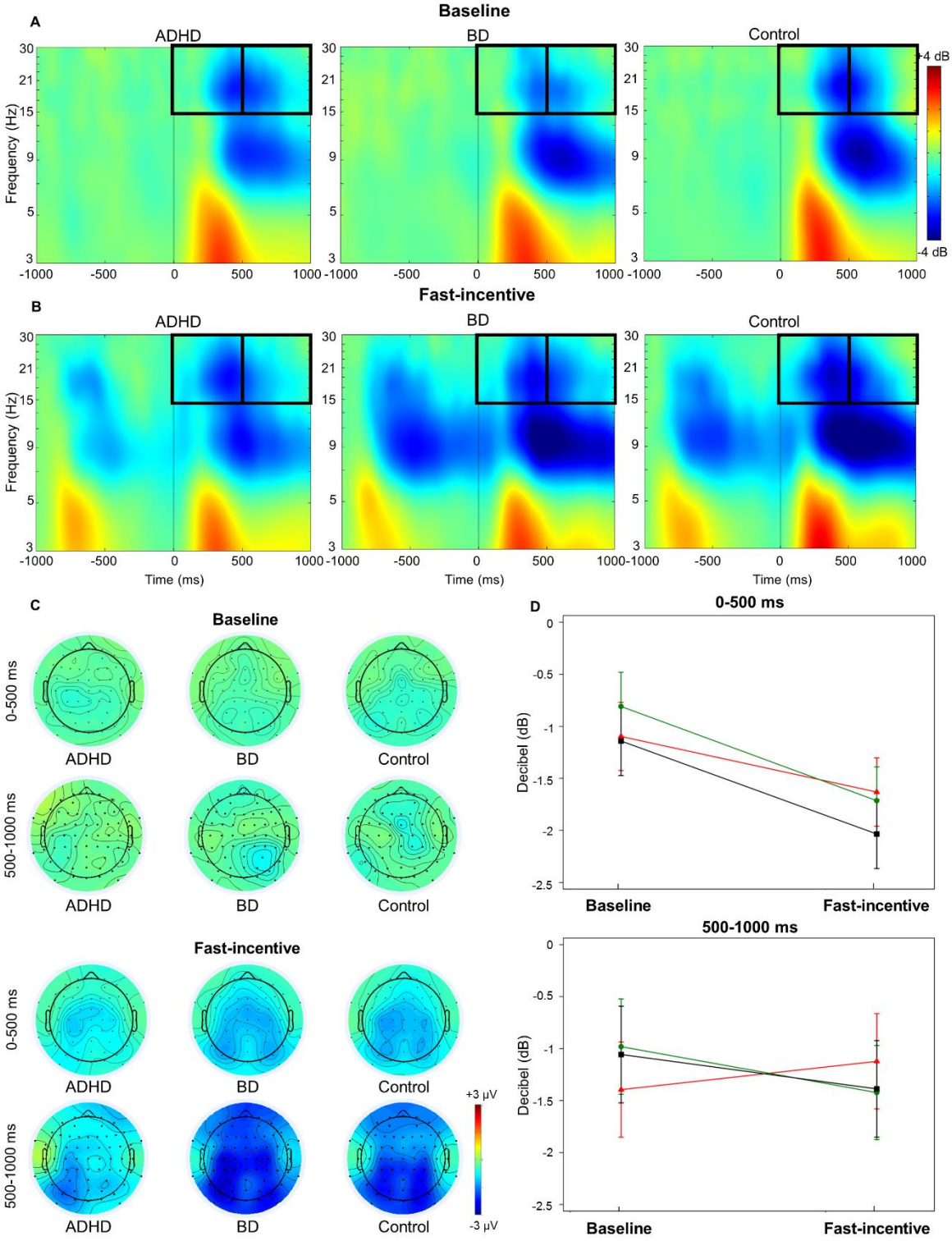

Figure 6.3. *Beta event-related spectral perturbation (ERSP) at central regions in the ADHD, BD and control groups in the baseline and fast-incentive conditions of the Fast task. (A) ERSP in the baseline condition; (B) ERSP in the fast-incentive condition; (C) Topographic maps by group in the 0-500 ms and 500-1000 ms windows at each condition; (D) Condition effects in at each time window by group (ADHD group in red, BD group in green, control group in black).*

6.4.4 Theta phase consistency (ITC)

A main effect of group ($p=0.03$) and condition ($p<0.001$), but no group-by-condition interaction ($p=0.41$), emerged for theta ITC in the 0-500 ms window. Post-hoc tests showed no differences between groups in the baseline condition (Table 6.2). In the fast-incentive condition, theta ITC was significantly decreased (i.e., phase was more variable) in the ADHD and BD groups compared to the control group, with no differences between ADHD and BD groups (Figure 6.4). A significant within-group increase in theta ITC (i.e., decrease in phase variability) from the baseline to the fast-incentive condition emerged in the control and BD groups, and at trend-level in the ADHD group (Table 6.3), but no differences between groups emerged in the degree of change between conditions. Further analyses compared groups prior to target onset, and found no differences in theta ITC before target appearance (Appendix E).

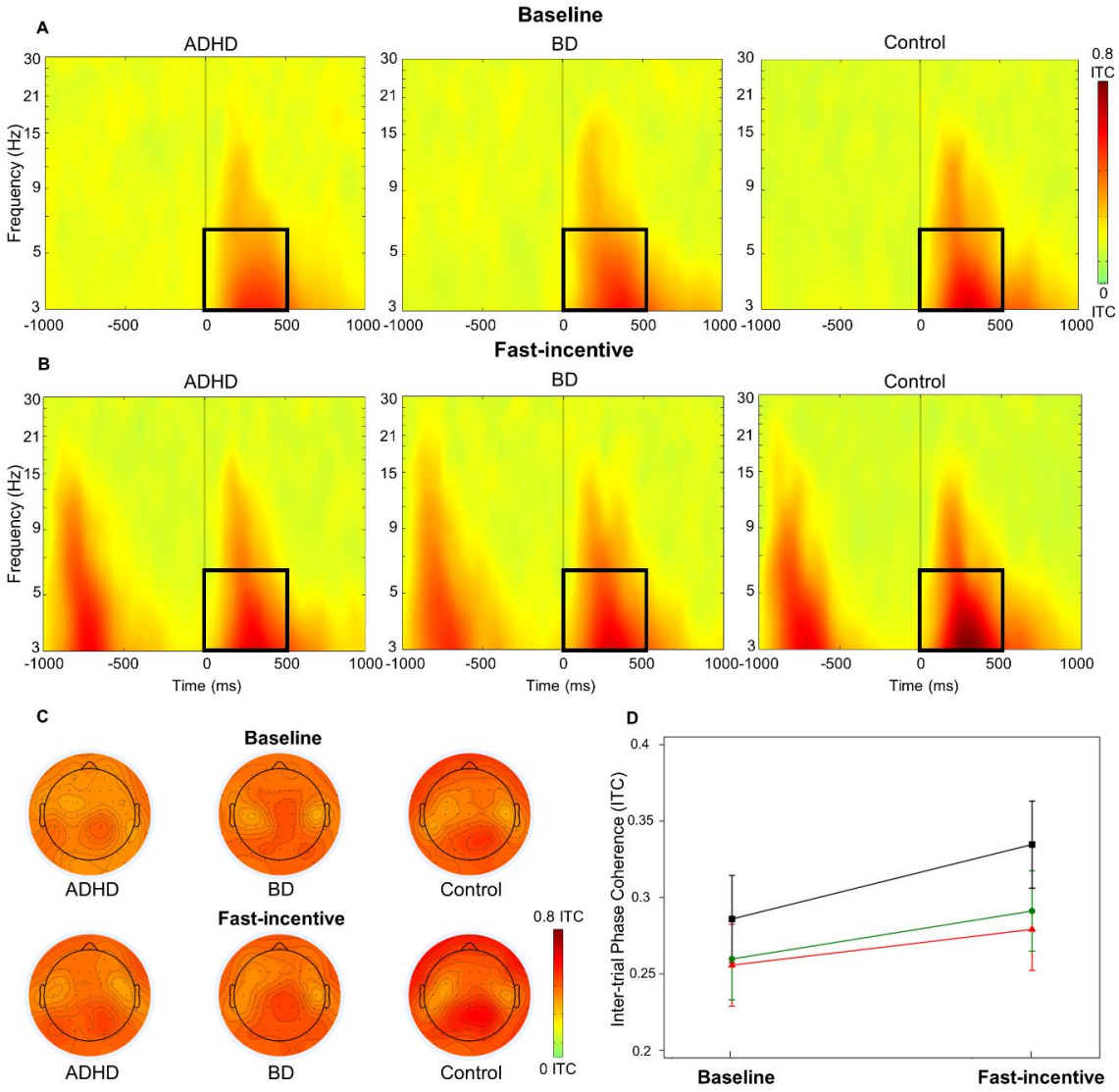

Figure 6.4. *Theta inter-trials phase coherence (ITC) at parietal regions in the ADHD, BD and control groups across the baseline and fast-incentive conditions of the Fast task. (A) ITC in the baseline condition; (B) ITC in the fast-incentive condition; (C) Topographic maps by group in the 0-500 ms window at each condition; (D) Condition effects in the 500-1000 ms window by group (ADHD group in red, BD group in green, control group in black).*

Table 6.2. Group comparison of cognitive and EEG measures in the baseline and fast-incentive condition

	Baseline condition						**Fast-incentive condition**					
	ADHD vs BD		**ADHD vs Ctrl**		**BD vs Ctrl**		**ADHD vs BD**		**ADHD vs Ctrl**		**BD vs Ctrl**	
	d	**p**	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**	**d**	**p**
RTV	0.19	0.544	**0.82**	0.016*	*0.69*	0.040*	0.20	0.541	*0.75*	0.027*	*0.66*	0.050*
CNV	0.02	0.937	0.08	0.821	0.05	0.876	*0.56*	0.089†	**1.41**	<0.001**	*0.69*	0.044*
P3	0.02	0.954	0. 11	0.736	0.11	0.751	0.13	0.686	0.44	0.193	*0.56*	0.099
Theta ERSP (0-500 ms, CP)	0.08	0.818	0.20	0.561	0.11	0.735	0.11	0.729	0.23	0.497	0.31	0.353
Theta ERSP (0-500 ms, FC)	0.31	0.341	0.06	0.859	0.17	0.614	0.19	0.565	0.25	0.462	0.41	0.221
Alpha ERSP (0-500 ms)	0.30	0.368	0.39	0.389	0.13	0.967	*0.50*	0.129	0.48	0.160	0.04	0.908
Alpha ERSP (500-1000 ms)	0.29	0.382	0.31	0.363	0.04	0.896	0.27	0.399	*0.78*	0.026*	0.44	0.191
Beta ERSP (0-500 ms)	0.38	0.251	0.17	0.613	*0.52*	0.129	0.10	0.764	*0.56*	0.105	0.38	0.248
Beta ERSP (500-1000 ms)	0.35	0.309	0.46	0.179	0.02	0.943	0.30	0.362	0.30	0.378	0.04	0.905
Theta ITC	0.09	0.787	0.47	0.168	0.43	0.199	0.17	0.600	**0.83**	0.018*	*0.72*	0.036*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CNV, contingent negative variation; CP, centro-parietal region; Ctrl, control group; d, Cohen's d; ERSP, event-related spectral perturbation; FC, fronto-central region; ITC, inter-trial phase coherence; MRT, mean reaction time; p, p value from random intercept linear models; RTV, reaction time variability.

*Notes: **p<0.01, *p<0.05, †p<0.09. Bold=large effect size (d≥.80); Italics=medium effects size (d≥.50)*

Table 6.3. Comparison of condition effects within group and between groups

	Within-group differences			Between-group differences					
	ADHD	BD	Ctrl	ADHD vs BD		ADHD vs Ctrl		BD vs Ctrl	
	p	p	p	d	p	d	p	d	p
RTV	<0.001**	<0.0001**	<0.001**	0.01	0.982	0.22	0.507	0.30	0.366
CNV	0.019*	<0.001**	<0.001**	*0.59*	0.083†	**1.17**	0.002**	*0.59*	0.088†
P3	0.723	0.331	0.026*	0.08	0.814	0.49	0.159	*0.68*	0.048*
Theta ERSP (0-500 ms, CP)	0.039*	0.003**	0.085†	0.19	0.567	0.03	0.930	0.21	0.543
Theta ERSP (0-500 ms, FC)	0.004*	<0.001**	0.056†	0.40	0.231	0.17	0.612	0.55	0.106
Alpha ERSP (0-500 ms)	0.001**	<0.001**	<0.001**	0.44	0.188	0.44	0.202	0.05	0.879
Alpha ERSP (500-1000 ms)	0.568	0.510	<0.001**	0.13	0.701	*0.71*	0.045*	*0.52*	0.132
Beta ERSP (0-500 ms)	<0.001**	<0.001**	<0.001**	*0.69*	0.044*	*0.72*	0.040*	0.05	0.885
Beta ERSP (500-1000 ms)	0.104	0.007**	0.054†	**1.05**	0.003**	**0.87**	0.014*	0.14	0.683
Theta ITC	0.083†	0.018*	<0.001**	0.16	0.634	0.43	0.216	0.30	0.379

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CNV, contingent negative variation; CP, centro-parietal region; Ctrl, control group; d, Cohen's d; ERSP, event-related spectral perturbation; FC, fronto-central region; ITC, inter-trial phase coherence; MRT, mean reaction time; p, p value from random intercept linear models; RTV, reaction time variability.

*Notes: **p<0.01, *p<0.05, †p<0.09. Bold=large effect size (d≥.80); Italics=medium effects size (d≥.50).*

6.5 Discussion

In this comparison between ADHD and BD on cognitive, ERP and brain-oscillatory markers of attentional processes, women with ADHD and women with BD showed overlapping impairments in fluctuations in attentional performance (RTV), neural variability (theta ITC) and neural response preparation (CNV). Individuals with either disorder further displayed a similar inability to adjust neural attention allocation (P3) and activation (alpha suppression) from a baseline to a fast-paced and rewarded condition, suggesting no adaptation to a changed context in these processes. Additional disorder-specific alterations in alpha and beta suppression were displayed by women with ADHD only, but impairments in most processes were shared between the two disorders. By examining both ERP and fine-grained brain-oscillatory indices of brain activity, these findings reveal novel neural mechanisms of shared attentional dysfunction in ADHD and BD, which potentially underlie some of the common symptoms in both disorders.

At the cognitive level, both ADHD and BD groups showed increased RTV in both task conditions, indicating more frequent fluctuations in response speed and impairments in the ability to sustain attention during the task. Increased RTV in both disorders is consistent with our results with this sample using a cued CPT task (Michelini et al., 2016b), and previous studies on ADHD (Cheung et al., 2016, Kuntsi et al., 2010, Kofler et al., 2013) and BD (Moss et al., 2016, Bora et al., 2006, Brotman et al., 2009). We further show novel evidence of intra-individual variability also at the neural level in the phase of theta oscillations in both women with ADHD and women with BD. Low phase variability over trials is thought to reflect an adaptive mechanism to maintain stable neural processing of a stimulus (Makeig et al., 2004a, Papenberg et al., 2013). The increased variability in theta oscillations, previously reported in adolescents with ADHD (Groom et al. 2010; McLoughlin et al. 2014), thus points to a reduced ability to maintain a consistent pattern in the timing of evoked theta response to targets over trials in adults with ADHD and BD (Cavanagh et al., 2009, McLoughlin et al., 2014b). Although these differences emerged as significant only in the fast-incentive condition, the group-by-condition interaction was not significant, suggesting that there may be subtle differences also in the baseline condition, non-significant in this sample. Further analyses in the pre-stimulus window indicated that, compared to individuals with ADHD or BD, control women displayed greater phase consistency upon target presentation, but lower consistency before targets. As such, with presentations of targets across trials, the controls displayed a consistent alignment and increase in consistency in the phase of theta (called phase resetting) (Palaniyappan et al., 2012, Lakatos et al., 2009) from the low consistency observed in the pre-stimulus window. This mechanism

may be lacking in women with either ADHD or BD as indicated by the more frequent fluctuations in this neural mechanism across trials. Overall, our findings of increased variability in cognitive and neural processes in women with ADHD or BD indicate an overlap in the neural underpinnings of impaired attentional fluctuations in both disorders, which may point to common neurobiological dysfunctions.

By further examining pre-stimulus response preparation in ADHD and BD, we found shared preparatory impairments, as indicated by reduced CNV, in both clinical groups in the fast-incentive condition. This finding is consistent with our previous results in this sample using a CPT task (Michelini et al., 2016b), and in adolescents and young adults with ADHD using the same task employed in this study (Cheung et al., 2017). Suggestive (trend-level) differences between ADHD and BD in this measure may also indicate more pronounced CNV impairment in ADHD, although this awaits replication in future studies. The pattern for P3 amplitude in response to targets, which was not different from controls in either ADHD or BD groups, indicates that women with either disorder may not be impaired in this ERP of attentional allocation. This result is consistent with our previous study with this sample (Michelini et al., 2016b), showing intact P3s following cue and target stimuli, and other previous studies reporting normal attentional P3 amplitudes in adults with ADHD (McLoughlin et al., 2010, Barry et al., 2009) or BD (Bestelmeyer, 2012). Yet, this P3 finding does not align with our previous larger-scale investigation using this task in ADHD, where our predominantly-male group of adolescents and young adults with ADHD (mean age: 18 years) showed a reduced P3 in the baseline condition (with a small effect size) compared to controls (Cheung et al., 2017). In the current study, the intact target P3 in ADHD may be due to gender or age, the present study being the first on this task using an all-female and all-adult sample (mean age: 37 years). In addition, the ADHD group had lower IQ than the control group in our previous study, and the ADHD-control difference on the P3 was non-significant when IQ was controlled for (Cheung et al., 2017). The lack of IQ differences between groups in the current sample may have contributed to the lack of group differences in the P3. Taken together, these findings indicate that both ADHD and BD are associated with reduced ERP activity of attentional preparation and anticipation of motor responses.

With faster target presentation and incentives, further shared impairments between ADHD and BD emerged in adjustments between conditions. These task manipulations, originally designed in ADHD studies to reward more consistent response times, produced comparable reductions in RTV in clinical and control groups. At the neural level, women with ADHD, and potentially (at trend-level) with BD, displayed significantly reduced increases in CNV amplitude compared to

controls, and no improvements in allocation of attentional resources (P3) (Polich, 2007) or attentional selection (alpha suppression) (Klimesch, 2012). The novel finding of a reduced ability to increase alpha suppression with task demands in both disorders points to a common inability in individuals with ADHD and BD to regulate brain activity implicated in attentional selection processes (Klimesch et al., 2007, Klimesch, 2012). A reduced adjustment in the response preparation CNV in women with ADHD replicates our previous findings in adolescents and young adults with the disorder (Cheung et al., 2017). Yet, in the P3, neither of the clinical groups showed the improvement between conditions displayed by controls. This pattern for the P3 contrasts with our previous findings using this task in a sample of adolescents and young adults with ADHD, where the ADHD group showed improvements between conditions in the P3, which were greater than those observed in the control group, suggesting malleability in this attentional ERP component in ADHD (Cheung et al., 2017). Similarly, these results in ADHD do not align with studies in children, adolescents and young adults indicating greater RTV malleability and improvements in ADHD than in neurotypical samples (Andreou et al., 2007, Kuntsi et al., 2009, Kuntsi et al., 2013, Cheung et al., 2017). A possible explanation for the inconsistencies in P3 and RTV adjustments is the age difference between the samples of current and previous studies: it could be hypothesised that adults with ADHD, compared to younger individuals, may be less sensitive to task manipulations in these processes. Since this is the first study examining these processes in an all-female adult sample, gender effects represent another possible reason for these inconsistencies with previous studies, which used predominantly-male samples (Andreou et al., 2007), (Cheung et al., 2017). Finally, since the ADHD sample used in the current adult female study (n=20) was smaller than those used in previous studies (e.g., n=94, Cheung et al., 2017), the possibility remains that the task manipulation effects would emerge with larger sample sizes also in adult women with ADHD. Longitudinal studies and replications in larger samples, including individuals of both sexes, are needed to examine potential developmental and gender effects on the malleability of markers of attentional processes in ADHD.

While most impairments were shared between ADHD and BD, we further found impairments specific to ADHD. Women with the disorder displayed a dysfunction in attentional selection, as indexed by lower alpha power suppression in response to targets in the fast-incentive condition (Klimesch et al., 2007, Klimesch, 2012). These results are consistent with previous studies reporting attenuated event-related alpha suppression in ADHD (Hasler et al., 2016, Missonnier et al., 2013, Mazaheri et al., 2014, Lenartowicz et al., 2014). In addition, in the change from the baseline to the fast-incentive condition, individuals with ADHD were specifically associated with lower adjustments in the suppression of beta power than in individuals with BD and controls,

indicating reduced improvements in neural mechanisms associated with response execution (Mazaheri et al., 2014, Bickel et al., 2012). While the ADHD-specific impairment in alpha suppression did not distinguish women with ADHD from women with BD, the reduction in the adjustment in beta power suppression with task demands significantly differentiated the two clinical groups. The latter brain-oscillatory process may thus represent neurobiological dysfunctions specific to ADHD, which may potentially help delineate ADHD from BD in adults.

The following limitations should be considered when interpreting our findings. First, although the groups were matched on gender, age and IQ, there were differences in the prescribed medications that participants were taking. We asked participants with ADHD to stop taking stimulant medication 48 hours before assessments, but it was not possible, for ethical reasons, to ask participants to stop mood-stabilising, anti-psychotic or antidepressant medications. Medication effects are difficult to control for in cross-disorder studies where different groups are prescribed different treatments, resulting in a limited number of participants within medication subgroups. However, previous studies suggest that medication may show positive effects (reducing differences from controls) or no effects on cognitive-EEG measures (Anderer et al., 2002, Karaaslan et al., 2003, Galletly et al., 2005, Degabriele and Lagopoulos, 2017, Groom et al., 2013). As such, it is unlikely that the group differences reported in this study reflect confounding medication effects. Second, while the two task conditions were matched on number of trials, they differed in duration and in length of the fore-period between warning and target stimuli. While we obtained comparable findings in RTV with length-matched segments, ERP/EEG analyses could not be repeated on length-matched segments, as doing so would have produced insufficient number of trials in the baseline condition to obtain reliable ERP/EEG indices. In addition, the different fore-periods and the use of a 0.25 Hz high-pass filter may reduce comparability of preparatory activity between the conditions. Yet, the analysis of the CNV (showing typical topographies at central sites) and the further analyses of EEG activity in the warning-target interval under fast-incentive conditions (Appendix E) allowed detailed investigation of neural preparatory processes in this latter condition. Future studies could examine stimulus-related and preparatory processes in ADHD and BD using other tasks, as well as examine the influences on slower frequencies on the CNV. Finally, although the current study and previous analyses on this sample (Michelini et al., 2016b, Rommel et al., 2016) represent the most comprehensive comparisons between ADHD and BD on cognitive, ERP and EEG markers to date, the sample is relatively small. While several significant differences between groups emerged with medium-to-large effects with current sample sizes, larger studies are needed to investigate subtler impairments in ADHD and BD.

Taken together, these findings further our understanding of the neural underpinnings of attentional impairments in both disorders, and provide new evidence into the overlap and specificity of impairments in these processes in women with ADHD and BD. The shared markers of attentional dysfunctions may represent biomarkers for both disorders. The shared atypical neural profiles related to attentional processes may underlie similarities in behavioural symptoms (e.g., distractibility) between ADHD and BD, which can lead to difficulty in delineating between ADHD and BD and incorrect treatment decisions. Finally, since ADHD and BD show genetic overlap (Lee et al., 2013, van Hulzen et al., 2016, Song et al., 2015), and increased attentional fluctuations may represent candidate markers of genetic/familial risk for both disorders (Adleman et al., 2014, Kuntsi et al., 2010), future studies could examine whether shared genetic factors may underlie overlapping attentional dysfunctions in ADHD and BD.

CHAPTER 7 - General discussion and conclusions

7.1 Abstract

This concluding chapter provides a summary of the key findings from this thesis. Linking the findings from both parts of this thesis, I will consider the clinical and research implications of this body of work in relation to individuals with attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD). I will then review the strength and limitations of the studies included in this thesis, and discuss future directions. The thesis ends with final conclusions.

7.2 Summary of aims

The overall aim of this thesis was to study cognitive and neurophysiological impairments in ADHD in adolescence and adulthood, by examining their developmental and aetiological pathways to remission and persistence in adolescents and adults with childhood ADHD, as well as the specificity of these impairments to ADHD, in comparison to BD.

The first part of this thesis has investigated the developmental pathways of cognitive processes, brain activity and connectivity in relation to persistence and remission of ADHD. Clinical observations and previous studies of clinical samples have shown that ADHD persists, either in full or in partial remission, in the majority of individuals that receive a diagnosis in childhood (Cheung et al., 2015, Faraone et al., 2006, van Lieshout et al., 2016b). Yet, only few studies have previously aimed to understand what may be the mechanisms underlying the developmental outcomes of persistence and remission of ADHD in the transition to adolescence and young adulthood (Cheung et al., 2016, Biederman et al., 2009, Francx et al., 2015b). The first two studies focused on cognitive-performance, event-related potential (ERP) (Chapter 2) and brain connectivity (Chapter 3) measures during the arrow flanker task in relation to ADHD remission and persistence in a large sample of individuals with a childhood ADHD diagnosis and neurotypical individuals. Specifically, the aim of these two chapters was to examine whether the investigated measures are markers of remission, distinguishing ADHD “persisters” from “remitters”, or enduring deficits, unrelated to ADHD outcome. With the inclusion of the unaffected siblings of childhood ADHD probands, the aetiological structure of a broad range of

cognitive-neurophysiological impairments and ADHD was further investigated using a factor analysis and multivariate sibling model-fitting approach, to identify the aetiological pathways to impairments in persistent ADHD in adolescence and young adulthood (Chapter 4).

The second part of this thesis aimed to examine whether alterations in cognitive and neurophysiological processes in adults with ADHD are specific to the disorder, or may be shared with BD, which often co-occurs or presents certain areas of symptomatic overlap with ADHD. In particular, adults with ADHD and adults with BD may show similar symptoms of distractibility and impulsivity, as well as cognitive impairments in attentional and inhibitory processes, but only a few studies prior to this thesis have directly compared individuals with ADHD and individuals with BD (Kitsune et al., 2016, Rommel et al., 2016). Cognitive and neurophysiological profiles in adults with ADHD, adults with BD and control adults were investigated, in order to identify distinct and shared cognitive and neurophysiological impairments in the two disorders. Groups were compared on cognitive-ERP (Chapters 5 and 6) and brain-oscillatory (Chapter 6) markers of attentional and inhibitory processes from the cued continuous performance task (CPT-OX), and of attentional fluctuations in the Fast task, a four-choice reaction time task. Shared alterations in cognitive and brain function can inform on the neurobiological pathways that are common between the two disorders, while distinct alterations may aid diagnostic delineation, which in some cases can be difficult due to symptomatic similarities between the two conditions. A further aim of the second part of this thesis was to provide new empirical data on impairments in these processes in females with ADHD, as the majority of previous studies have been conducted in male-only or predominantly-male samples (Albrecht et al., 2008, McLoughlin et al., 2009, Cheung et al., 2016, Kuntsi et al., 2010), due to the higher prevalence of ADHD in males than females in childhood (Ramtekkar et al., 2010, Willcutt, 2012).

7.3 Key findings

7.3.1 Neurophysiological error detection on attention-vigilance processes are markers of ADHD remission

The first study in this thesis (Chapter 2) sought to investigate cognitive and neurophysiological measures during a performance monitoring task with congruent (low conflict) and incongruent (high conflict) conditions in a follow-up study of 110 adolescents and young adults with childhood ADHD and 169 age-matched control participants. The results show that ADHD

remitters did not differ from control individuals, but showed more typical profiles compared to ADHD persisters in cognitive measures of attention-vigilance processes and neurophysiological markers of error processing. Given this pattern of results, these measures may represent markers of remission. Specifically, ADHD persisters showed greater reaction time variability (RTV) and number of errors in the low-conflict condition, likely reflecting impairments in attention-vigilance processes, compared to both ADHD remitters and controls, with the latter two groups showing indistinguishable profiles from one another. The same pattern of results emerged for ERP measures of automatic and conscious error processing (ERN and Pe, respectively), which were similarly associated with ADHD remission, with ADHD persisters showing reductions in these measures compared to both ADHD remitters and controls. In dimensional analyses within the childhood ADHD group, most of these measures were further associated with the continua of ADHD symptoms and functional impairments at follow-up.

The results of this study further show that ADHD remitters displayed intermediate profiles and no significant differences from persisters and controls in incongruent errors (reflecting executive control) and mean reaction time (MRT) in this highly effortful task (reflecting processing speed). Such findings suggest that incongruent errors and MRT, despite showing differences between ADHD persisters and controls, were not sensitive to the different ADHD outcomes at follow-up. Neurophysiological conflict monitoring (N2) in the incongruent condition similarly showed significant reductions in ADHD persisters, suggesting suboptimal processing of conflicting stimuli, but no differences between the two childhood ADHD groups.

The findings of this study extend previous results in this sample using cognitive-EEG measures from the CPT-OX and Fast task, as well as measures of IQ and digit span (Cheung et al., 2016). In this earlier study, measures of preparation-vigilance processes (RTV, omission errors, contingent negative variation [CNV], and delta and theta activity) were markers of remission, whilst measures of executive processes (commission errors, digit span backward, NoGo-P3) were not sensitive to ADHD remission or persistence. Taken together, these results indicate that potentially more automatic non-executive cognitive processes, such as preparation-vigilance, and neurophysiological error processing are associated with remission of ADHD from childhood to adulthood, while more executive processes may be unrelated to ADHD outcome.

7.3.2 Atypical brain connectivity in adolescents and young adults with remitted and persistent ADHD

A subsequent analysis of the EEG data from the same arrow flanker task employed a brain-wide functional connectivity approach to examine brain connectivity in relation to ADHD outcomes of persistence and remission (Chapter 3). Results indicate that individuals with persistent ADHD, compared to controls, show widespread over-connectivity alterations and reduced ability to modulate connectivity with task demands. Specifically, ADHD persisters showed increased connectivity in theta, alpha and beta oscillations in a pre-stimulus window before target onset, as well as during target processing in the beta band. Increased EEG connectivity in the investigated frequency ranges may reflect exaggerated communication between brain regions, both during the inactive pre-stimulus period and during cognitive target processing. Considering the high cognitive demands induced by the high-conflict incongruent stimuli in this highly effortful task, where a response at every trial is required, enhanced connectivity in individuals with ADHD, especially in the beta frequency band, may reflect over-connectivity in brain networks underlying executive control. The persistent group further showed a reduced adjustment of connectivity in the theta band with appearance of the target between the pre-stimulus and the post-stimulus window. This pattern of results may point to a dysfunctional regulation of brain network connectivity in slow oscillations in individuals with ADHD, and reduced ability to modulate brain connectivity patterns from a relatively inactive context to a condition requiring higher cognitive engagement.

Individuals with remitted ADHD did not differ from ADHD persisters in any measure, but showed significant differences from controls in connectivity measures of network integration and in all measures of change between pre-stimulus and post-stimulus windows. In line with results of categorical analyses, the investigated brain connectivity markers showed little evidence of dimensional associations with the continua of ADHD symptoms and functional impairment within individuals with childhood ADHD. These findings indicate that hyper-connectivity and reduced ability to modulate connectivity with task demands characterise adolescents and young adults with both persistent and remitted ADHD. Atypical functional connectivity during cognitive control processes may thus represent an enduring deficit in adolescents and adults with childhood ADHD, irrespective of their current diagnostic status. These findings extend the results presented in Chapter 2 and in a previous investigation using the same sample (Cheung et al., 2016), where the majority of investigated measures that were sensitive to impairments in ADHD persisters showed a pattern of markers of remission, distinguishing ADHD remitters from

persisters. Conversely, in this connectivity study, the findings point to a lack of differences between ADHD remitters and persisters in brain connectivity, with remitters showing, similar to persisters, neural alterations indicating over-connectivity and reduced modulation of connectivity with task demands.

A further finding from this study is that, while connectivity alterations emerged in ADHD groups before and during processing of trials where a correct behavioural response was made, differences between groups were largely lacking when participants in any group made an incorrect response. In particular, while the ADHD groups showed widespread over-connectivity alterations compared to controls across all frequency bands before the onset of targets prior to making a correct response, neither group differed from the control group in error responses. In addition, increased connectivity was observed prior to and during error responses compared to correct responses in all groups, further indicating that higher EEG connectivity may be suboptimal during this task. These findings thus suggest that atypically increased EEG connectivity in this task may lead to an error, both in neurotypical individuals and in individuals with persistent or remitted ADHD.

7.3.3 Aetiological structure of cognitive-neurophysiological impairments in ADHD in adolescence and young adulthood

The different developmental patterns observed for different types of impairments in cognitive and brain function in relation to ADHD outcomes may suggest a separation in the aetiological pathways leading to these alterations in ADHD. Previous studies in children with ADHD have shown that separable familial factors may underlie cognitive dysfunctions in the disorder (Frazier-Wood et al., 2012, Kuntsi et al., 2010, Wood et al., 2011), but no study prior to this thesis has examined the aetiological factor structure of cognitive impairments in ADHD in adolescence and young adulthood. Using a multivariate sibling model-fitting approach, this thesis extends previous studies by (1) examining these cognitive processes in adolescents and young adults with persistent ADHD, their unaffected siblings and control sibling pairs, and by (2) also including neurophysiological (ERP) measures (Chapter 4). Among the widespread cognitive and neurophysiological impairments that were associated with ADHD in this sample in previous studies (Cheung et al., 2016, Cheung et al., 2017) and in this thesis (Chapter 2), multivariate analyses were restricted to measures showing the strongest phenotypic overlap with ADHD and evidence of underlying familial influences, as indicated by phenotypic similarity between siblings in a same pair. Based on this first preliminary step, multivariate analyses examined the

aetiological factor structure of ADHD and impairments in a variety of processes associated with ADHD, including intelligence (IQ), short-term and working memory (digit span forward [DSF] and backward [DSB]), response speed (MRT) and variability (RTV), sustained attention (omission errors [OE], congruent errors [CongE]), inhibitory control (NoGo-P3), and error processing (ERN).

Factor analysis and sibling model-fitting approaches were applied to study the aetiological structure of impairments in these measures and ADHD in terms of familial and non-familial influences, representing the combined contribution of the genetic and environmental influences shared within sibling pairs, and individual-specific influences, respectively. Three familial factors emerged, underlying the association between impairments in these measures and ADHD. The familial factors captured: (1) response speed (MRT), response variability (RTV), and IQ; (2) short-term (DSF) and working (DSB) memory; and (3) sustained attention (OE, CongE), error processing (ERN) and, to a smaller extent, response inhibition (NoGo-P3). This factor structure points to a separation between familial influences accounting for measures of IQ and RT performance, measures of memory performance, and measures of response accuracy and brain activity of inhibition/error processes. The familial influences underlying ADHD overlapped strongly with both the first and third factors, and moderately with the second factor. Three factors also emerged for non-familial influences, with the only exception that IQ clustered with measures of memory rather than response speed and variability. These findings indicate a partial separation in the aetiological processes underlying cognitive-neurophysiological impairments in persistent ADHD, which may explain individual differences between individuals with the disorder in these processes. These results provide novel insights into the aetiological pathways to widespread impairments in cognitive and brain function, showing a multifactorial architecture of such alterations in ADHD in adolescence and adulthood. These findings extend evidence from studies in childhood, by examining an older age group but also including a broad range of cognitive and neurophysiological impairments, rather than only cognitive-performance measures, as in previous childhood studies (Frazier-Wood et al., 2012, Kuntsi et al., 2010, Wood et al., 2011).

7.3.4 Disorder-specific and shared impairments in ERPs of attention and inhibitory processes in ADHD and BD

The first study of the second part of this thesis investigated whether cognitive-neurophysiological measures of attention and inhibition differ between ADHD and BD, to identify impairments that are specific to either disorder or shared between ADHD and BD. Three groups of 20 women with ADHD, 20 women with BD and 20 control women were compared on

cognitive-performance measures (MRT, RTV, OE and commission errors [CE]) and ERPs of attentional orienting (Cue-P3), response preparation (CNV), conflict monitoring (NoGo-N2), response inhibition (NoGo-P3) and response execution (Go-P3) from the CPT-OX. The results showed that both ADHD and BD groups displayed a reduced NoGo-P3, indicating atypical inhibitory control, compared to controls. The CNV, reflecting ERP activity of response preparation, was significantly reduced in women with ADHD, and at trend level in women with BD, compared to controls. These findings indicate overlapping impairments in inhibitory control and, potentially, in response preparation in ADHD and BD. Instead, the N2 in response to NoGo stimuli, indexing conflict monitoring, was attenuated in women with BD only, compared to women with ADHD and controls. This neurophysiological alteration in conflict monitoring may thus be specific to BD and insensitive to impairments in ADHD in this task that induces low conflict demands (McLoughlin et al., 2010), unlike tasks inducing higher conflict demands, which are sensitive to N2 impairments in ADHD (McLoughlin et al., 2009, Chapter 2). Since the NoGo-N2 reduction in women with BD was temporally followed by the inhibitory control deficit in the NoGo-P3, this pattern may indicate broader alterations in both conflict and inhibitory processes in BD, among the processes implicated in withholding an incorrect response. Instead, women with ADHD only displayed the latter alteration, which suggests impairments primarily in response inhibition in women with ADHD during the processing of NoGo trials. Neither women with ADHD nor those with BD showed impairments in P3 components in response to Cue or Go stimuli, indicating potentially intact brain activity underlying attentional orienting and attentional allocation with response execution in women with either disorder.

Along with neurophysiological alterations, impairments in ADHD or BD, or both, emerged also in measures of cognitive performance. Specifically, relative to controls, women with ADHD showed increased OE and CE, and potentially higher (at trend level) RTV, while women with BD showed significantly increased RTV and potentially increased (at trend level) OE. Yet, none of these cognitive-performance indices differentiated women with ADHD from women with BD. This pattern of results may suggest greater ability of neurophysiological markers compared to cognitive-performance measures in detecting differences between individuals with ADHD and individuals with BD.

7.3.5 Shared and disorder-specific event-related brain oscillatory markers of attentional dysfunction in ADHD and BD

A second study on the same sample (Chapter 6) focused on attentional dysfunction in ADHD and BD. Individuals with either disorder were compared on measures of brain-oscillatory modulations of power and phase variability from EEG data, as well as RTV and ERPs, during a reaction time task under slow-unrewarded baseline and fast-incentive conditions. The results of this study indicate that both women with ADHD and women with BD showed increased RTV in the baseline condition and increased RTV, theta phase variability and reduced CNV in the fast-incentive condition. These findings point to overlapping alterations in increased fluctuations in attentional performance, neural variability and neural response preparation in women with ADHD and women with BD. Similar to the attentional P3 components examined in Chapter 5 (Cue- and Go-P3) with this sample, the P3 was intact in both clinical groups in both conditions of this task. In addition, while increased RTV and reduced CNV have been previously reported in both disorders, this chapter provides new evidence for increased intra-individual neural variability in the phase of theta oscillations in both women with ADHD and women with BD. Low phase consistency over trials points to a suboptimal ability to maintain a consistent pattern over trials in theta responses to targets in adults with ADHD and BD (Cavanagh et al., 2009, McLoughlin et al., 2014b, Groom et al., 2010a). Although this atypical theta phase variability emerged as significant only in the fast-incentive condition, the lack of a group-by-condition interaction may suggest that there may be subtle differences also in the baseline condition, non-significant in this sample. Further similarities between ADHD and BD emerged in the ability to adapt cognitive and neural profiles to a changed context, from a slow, unrewarded condition to a fast and incentivised condition. Both individuals with ADHD and with BD, unlike controls, failed to display an improvement between conditions in neural attention allocation (P3) and attentional selection and activation (suppression of alpha power). This shared alteration may index a similar inability of women with either disorder to adapt these neural processes to a changed context.

Additional impairments emerged in women with ADHD only. Specifically, women with the disorder showed reduced alpha suppression in the fast-incentive condition and lower adjustment in beta suppression between conditions relative to controls. These alterations in ADHD may indicate additional impairments in a brain-oscillatory marker of attentional selection (alpha suppression) and reduced improvements between conditions in neural mechanisms associated with response execution (adjustment in beta suppression). Yet, only the adjustment

in beta suppression distinguished between ADHD and BD, as impairments in most processes were shared between the two disorders

Overall, by examining both ERP and fine-grained brain-oscillatory indices of brain activity and variability, these findings reveal novel neural mechanisms of shared attentional dysfunction in ADHD and BD. The overlapping impairments in neural markers identified in this study may represent shared neurobiological mechanisms underlying attentional dysfunction in ADHD and BD. One prediction from these findings is that the common neural impairments may underlie some of the common symptoms typical of both disorders, such as distractibility.

7.4 Wider implications

7.4.1 Mechanisms underlying remission and persistence of ADHD

Two studies in this thesis (Chapters 2 and 3) provide new insights into the processes that may be markers of remission from ADHD, distinguishing between individuals with remitted and persistent ADHD, or enduring deficits, showing atypical profiles in both groups. Processes of attention-vigilance and neurophysiological error processing emerged as markers of remission from ADHD, and may represent cognitive and neural mechanisms linked to decline in ADHD symptoms and impairments from childhood to adolescence and early adulthood. A clinical implication of these findings is that these markers may be suitable targets for the development of new interventions for ADHD, such as those based on cognitive training and neurofeedback. Future studies should examine whether improvements in these processes following interventions may promote remission from the disorder and prevent detrimental long-term outcomes in individuals with a childhood diagnosis. Conversely, cognitive measures of executive control, neurophysiological conflict monitoring and functional connectivity were not sensitive to ADHD outcome, as they did not distinguish between individuals with remitted and persistent ADHD. Among these measures, atypical connectivity profiles (hyper-connectivity and reduced adjustment in connectivity with task demands) may further represent enduring deficits despite clinical remission, as remitters differed from neurotypical individuals in some of these measures, but were indistinguishable from persisters. Since these measures do not seem to follow the reduction with development in ADHD symptoms and impairment, it is possible that they may not represent good candidate targets for new interventions for ADHD.

Overall, initial convergence across cognitive and neurophysiological markers of ADHD persistence and remission is starting to emerge between studies from the follow-up sample used in this thesis (Chapters 2 and 3; Cheung et al., 2016, James et al., 2017) and previous studies (Pazvantoglu et al., 2012, McAuley et al., 2014, Biederman et al., 2009, Roman-Urrestarazu et al., 2016). Most measures showing the pattern of markers of remission may map onto largely non-executive processes, such as vigilance, preparation and attentional allocation, which potentially reflect lower-level or more bottom-up mechanisms (Chapters 2; Cheung et al., 2016, James et al., 2017). Instead, the majority of measures unrelated to ADHD outcome (Chapters 2 and 3) may reflect more executive or top-down cognitive and neural processes, in line with most longitudinal studies of executive functions to date (Pazvantoglu et al., 2012, McAuley et al., 2014, Biederman et al., 2009, Roman-Urrestarazu et al., 2016).

The empirical data on the separation between these impairments in relation to ADHD remission may be related to studies showing improvements in RTV and ERPs of error processing under certain context manipulations, such as rewards and faster event rate, where children and adolescents with ADHD show greater improvements than neurotypical individuals (Kuntsi et al., 2009, Uebel et al., 2010, Groom et al., 2013, Andreou et al., 2007). Improvements in these indices in individuals with ADHD have further been shown with ADHD stimulant medication (Rhodes et al., 2006, Bron et al., 2014, Groom et al., 2013). An improvement with incentives, conversely, has not been shown in measures of executive function, such as CE (Kuntsi et al., 2009, Uebel et al., 2010), and more inconsistent evidence exists on the effect of medication on executive impairments (Scheres et al., 2003, Rhodes et al., 2006). These studies indicate that response variability and error processing are malleable and may improve with the additional allocation of cognitive arousal and motivational incentives in ADHD samples, while impairments in executive functions may be more “fixed” and less malleable. Taken together, the results on ADHD remission and on improvements in neurocognitive impairments with incentives may lead to the hypothesis that the more malleable non-executive or bottom-up processes may be more sensitive to developmental improvements and to positive environmental influences (e.g., high SES, supportive family environment) that may promote remission in a subgroup of individuals with childhood ADHD. Instead, the more fixed and less malleable executive impairments may be less sensitive to such influences, and represent risk factors or characteristics associated with the disorder in childhood (Johnson, 2012), which may not follow the developmental improvements in clinical symptoms in individuals that remit from the disorder. Yet, the follow-up studies included in this thesis and the majority of previous studies on ADHD remission are in conflict

with a prominent developmental theory of ADHD (Halperin and Schulz, 2006), which proposes that the remission or persistence of ADHD from childhood to adulthood would be predicted by the degree of maturation and improvement over time in prefrontally-mediated executive functions, which could act as mechanisms of compensation. Conversely, lower-level functions would be linked to the presence of ADHD in childhood, irrespective of later clinical status, according to this model (Halperin and Schulz, 2006). Future studies are needed to formally test the hypotheses presented here and refine theoretical developmental models of ADHD based on available empirical evidence.

7.4.2 Multiple pathways to cognitive-neurophysiological impairments in ADHD

The study into the aetiological structure of cognitive-neurophysiological impairments in ADHD in adolescence and early adulthood (Chapter 4) indicates a partial separation between three processes, accounting for IQ and response speed/variability, short-term and working memory, and sustained attention and error/inhibition processes. Alterations in cognitive processes and brain activity may thus result from multiple atypical neurobiological pathways, supporting theoretical models that emphasise the role of multiple functions in the pathogenesis of ADHD (Halperin and Schulz, 2006, Castellanos et al., 2006). This multifactorial structure may explain the observed heterogeneity in cognitive profiles that exists among individuals with ADHD (Mostert et al., 2015, Coghill et al., 2014), who display various degrees of impairments in several cognitive functions. The partial aetiological dissociation between the identified cognitive clusters in ADHD may indicate that impairments in these factors have different roles in relation to ADHD pathophysiology. For example, only some impairments may represent mediators lying on the causal pathways to ADHD, while others may only represent associated characteristics (Kendler and Neale, 2010).

A possible clinical implication of these findings is that, in the development of new non-pharmacological treatments for ADHD, such as those based on cognitive training and neurofeedback, multiple processes could be targeted by different intervention components, and tailored based on the specific impairments manifested by each individual, with a personalised approach. Yet, limited evidence exists on the fact that interventions targeting cognitive processes can an effect on ADHD symptomatology (Cortese et al., 2015). In particular, it has been shown that treatments targeting working-memory impairments have limited-to-no effects on ADHD symptoms (Cortese et al., 2015). The results of non-familial influences on the identified factors may provide an explanation for the lack of efficacy of working-memory training

programmes. At the non-familial level, the variance of most measures, including working memory, was largely captured by measure-specific influences, which were not shared with ADHD. In sibling model fitting, non-familial influences include individual-specific environmental factors, representing any differences in the environment between siblings, and may also include the effects of any treatment for ADHD. Since the memory or response-accuracy processes appear to be captured by aetiological influences that are largely not shared with those on ADHD, any improvement in these measures may not mediate or moderate improvements in ADHD. Conversely, the non-familial variance of MRT and RTV was almost entirely accounted for by a non-familial factor which moderately overlapped with non-familial influences on ADHD, with limited residual variance in these measures not shared with the disorder. A possible prediction is that non-pharmacological cognitive training interventions aimed at alleviating ADHD symptoms may be more effective if they target reaction time processes rather than memory or response accuracy. This is in line with the evidence that RTV in children and adolescents may be more malleable than executive processes (Kuntsi et al., 2009, Uebel et al., 2010), and that RTV is associated with ADHD remission in follow-up studies (Chapter 2; Cheung et al., 2016).

7.4.3 Modulation of neural processes with task demands in ADHD and BD

The findings from two of the studies included in this thesis (Chapters 3 and 6) suggest that individuals with ADHD or BD may show reduced modulations of neural processes with task demands. Controls showed increases in P3 and alpha power suppression in changing from a slow, unrewarded task condition to a faster and incentivised condition in the Fast task. Instead, adults with ADHD or BD showed a lack of adjustment between conditions in both measures (Chapter 6). These alterations in brain activity of attentional allocation and attentional selection, respectively, may indicate that these attentional processes in adult women with ADHD or BD are less sensitive than in controls to the manipulations of this task. This finding may point to lower malleability in these neural processes in adults with ADHD or BD with changed task demands. This interpretation is further supported by the pattern of findings of atypically increased neural variability in the phase of theta oscillations in both clinical groups, also pointing to an altered modulations of brain processes in both ADHD and BD. Specifically, women with ADHD and women with BD, compared to controls, showed a lower increase in theta phase consistency over trials in switching from a preparatory (pre-stimulus) to a cognitively active (post-stimulus) condition upon target appearance. This process has previously been referred to as “phase-resetting” (Palaniyappan et al., 2012, Lakatos et al., 2009). Significantly more variable event-related theta phase responses over trials were further observed in both clinical groups relative

to controls in the fast-incentive condition, but not in the baseline condition. Phase-resetting in theta responses over trials has been suggested as a mechanism underlying enhancements of P3 components after stimulus presentation in cognitive tasks, along with increases in allocation of brain activity (Mazaheri and Picton, 2005, Basar-Eroglu et al., 1992). As such, the results of atypical phase consistency and P3 in this study may converge in indicating reduced sensitivity to task manipulations in adults with ADHD or BD.

The lack of modulation in neural processes with task demands in adults with ADHD and adults with BD may be linked to results of previous studies, indicating a lack of adaptation in theta power in switching from a resting state condition to the CPT-OX task in adults with ADHD or with BD (Rommel et al., 2016, Skirrow et al., 2015). The lack of such a neural mechanism could indicate a reduced ability to modulate brain activity with changing cognitive demands (Rommel et al., 2016, Skirrow et al., 2015). A similar alteration to that observed in these resting-to-task studies could also underlie the lack of modulation in the P3 and suppression of alpha power in Chapter 6, both linked to attentional processes, in changing from the baseline condition, where participants spend the majority of time in a condition similar to "resting", to the fast-incentive condition that has an event rate more similar to that of other attentional tasks, such as the CPT-OX (Rommel et al., 2016, Skirrow et al., 2015). The atypical modulations in theta activity in changing from resting to active attentional states have been hypothesised to be related to alterations in the default-mode network (DMN) (Rommel et al., 2016, Skirrow et al., 2015), as studies in ADHD have shown that the DMN may be inadequately suppressed during cognitive tasks (Cortese et al., 2012). Future studies, potentially combining EEG and fMRI techniques, are needed to test whether DMN alterations underlie impairments in adapting to context changes in ADHD and BD.

Adolescents and young adults with ADHD further showed a reduced modulation in brain connectivity in theta oscillations from a pre-stimulus condition to an actively engaging cognitive processing condition, following target onsets in high-conflict trials of the arrow flanker task (Chapter 3). This finding suggests that individuals with the disorder have difficulties in adapting their connectivity profiles in slow oscillations to task demands in this highly effortful task. Previous studies have associated connectivity in theta oscillations during cognitive tasks with cognitive processes engaging control networks and requiring co-ordination of activity between distributed brain areas (Buzsaki and Draguhn, 2004, Uhlhaas and Singer, 2006, Wang, 2010). Given the high levels of cognitive control enhanced by incongruent stimuli in this task, the modulation from pre-stimulus to post-stimulus windows of theta connectivity may have a role

in co-ordinating activity between various regions of the executive network and maintaining optimal cognitive control during the task. Alterations in modulating theta connectivity in ADHD may point to dysfunctional regulation of slow oscillations in brain networks of executive control, and to an inability to adapt brain connectivity from a relatively-inactive context to a condition requiring cognitive engagement. An alternative explanation for the reduced modulation of theta connectivity, as discussed above, is a dysfunctional modulation of the DMN in individuals with ADHD, who may engage in irrelevant cognitive activities (e.g., mind wandering) before stimulus onset (Mowlem et al., 2016, Jonkman et al., 2017), potentially producing reduced preparation for the upcoming stimulus. Yet, the inter-stimulus interval (1.65 s) in the fast-paced task used in this study may be too short to allow participants to reach a neural condition similar to rest. An atypical modulation of connectivity linked to executive networks is thus a more likely explanation. Future studies performing similar pre-stimulus/post-stimulus comparisons in other tasks mapping onto potentially less executive processes, as well as examining connectivity between brain regions with more precise spatial resolution, will be useful to clarify this matter further.

7.4.4 Developing biomarkers for ADHD and BD

The diagnosis of ADHD and BD, similar to other psychiatric diagnoses, is based on clinical observations and descriptions of behavioural symptoms. The subjective nature of such indices contrasts with the more objective indicators and diagnostic tools that are commonly used in other branches of medicine to assign diagnoses and monitor treatment outcomes, in conjunction with reports on symptoms. The identification of objective markers of alterations at the cognitive and neurophysiological levels, together with being useful for understanding the mechanisms underlying clinical symptoms and impairment, may have future clinical applications, as they may aid in diagnostic and treatment decisions (Jeste et al., 2015). The identification of biomarkers for psychiatric disorders with high sensitivity and specificity may help parse the complexity of the clinical manifestations of these conditions and aid in disease prediction, diagnosis, and treatment monitoring in addition to behavioural symptoms (Loo and Makeig, 2012, Loo et al., 2015, McLoughlin et al., 2014a). Amongst putative biomarkers, objective measures derived from high-density electroencephalography (EEG) may hold practical advantages as clinical biomarkers (Jeste et al., 2015, Loo et al., 2015): they are non-invasive, cost-effective, sensitive to individual differences in behaviour (Loo and Makeig, 2012, Loo et al., 2015, McLoughlin et al., 2014a), and provide the millisecond temporal resolution necessary to capture fast-changing cognitive and neural functions (Jeste et al., 2015, Loo et al., 2015).

The second part of this thesis includes two cross-disorder neurophysiological studies in ADHD and BD, aimed at finding objective measures of differences and similarities between the two disorders. In Chapter 5, evidence emerged for differences in conflict monitoring (NoGo-N2) between women with BD and women with ADHD, as only the former group showed impairments in this process in this task inducing low levels of conflict-monitoring demands. In Chapter 6, a further difference between the disorders was observed in a measure of change between a slow, unrewarded condition to a fast, incentivised condition, as women with ADHD showed a lower increase between conditions in suppression of beta power, reflecting a lower improvement between conditions in neural activity of motor execution, relative to women with BD. When referred for clinical consultation, some cases of ADHD or BD may present with certain overlapping symptoms of the two disorders, which may lead to uncertainty regarding the diagnostic boundaries and, in turn, treatment decisions. These initial results represent some of the first findings of potentially distinct neurophysiological profiles in ADHD and BD. If replicated in future studies with larger samples, the identified measures may represent candidate biomarkers to aid in the delineation of the diagnostic boundaries between the two disorders in adults. Yet, it remains unclear to what extent these candidate biomarkers for BD and ADHD may be specific to these two disorders, or rather shared with other psychiatric or neurodevelopmental diagnoses. Since the comparison with further disorders was not a focus of this thesis, future research is needed to clarify this issue. To move forward towards a potential clinical application of the identified measures as biomarkers to aid in diagnostic and treatment decisions, future studies could also explore whether combining markers from different domains (e.g., genetics, cognition and electrophysiology) may improve prediction relative to using a single domain.

7.5 Strengths and limitations

7.5.1 Sample sizes

The large size of the sample used in the first three chapters of this thesis is one of the main strengths of this work. The sample of individuals with childhood ADHD (n=110) and neurotypical individuals (n=169) used in Chapters 2 and 3 represents the largest study in ADHD that have used cognitive-ERP and EEG connectivity measures from a performance monitoring task. However, due to the high persistence rates of ADHD in this sample of adolescents and young adults, the sample size for the remitted ADHD group was modest (n=23) compared to the

persistent and control groups. As such, these results await replication in samples with greater numbers of remitted individuals. The full ADHD and control sibling-pair samples used in Chapter 4 consisted of 404 participants in total, making it one of the largest cognitive-EEG studies of ADHD to date.

The two cross-disorder comparison analyses of ADHD and BD used a sample of modest size (n=60 participants in total, 20 with ADHD, 20 with BD, 20 controls), as this study was originally designed as a pilot study to inform larger-scale investigations. Although medium-to-large effects were detected as significant with current sample sizes, this study may be limited in its ability of detecting more subtle differences between groups, which will require future larger-scale investigations.

7.5.2 Sibling model fitting

The analyses on the ADHD and control sibling-pair samples allowed to gain valuable insight not only into the association between ADHD and a range of cognitive-EEG alterations, but also to examine whether there are similarities or differences in certain traits between affected and unaffected siblings growing up in the same family. The advantage of having such information is that, in the presence of a phenotypic association between ADHD and other traits, one can then decompose their covariation into contributions of familial and non-familial factors, and thus examine aetiological pathways to the disorder. Yet, although sibling samples can estimate the aggregated contribution of familial effects on phenotypic similarities between siblings in the same family, they do not allow to distinguish between genetic and shared environmental factors. The contribution of genetic factors cannot thus be directly estimated with sibling samples, and should be tested in future studies using twin samples.

7.5.3 Categorical and dimensional definitions of ADHD

Another strength of this thesis is the use of both categorical and dimensional approaches to ADHD remission (Chapters 2 and 3). Specifically, categorical analyses compared individuals classified as ADHD persisters and remitters based on clinical cut-offs of ADHD as present or absent. Dimensional analyses examined how the investigated measures were associated with the continua of ADHD symptoms and impairments. Given the complexity of defining ADHD outcome based on categorical diagnosis or dimensional measures of ADHD symptoms and impairment, adopting both approaches is valuable to obtain a more complete picture of ADHD.

The former approach better reflects clinical diagnostic discriminations between affected and unaffected individuals. The latter approach uses symptom count and level of impairment as observed, thus not relying on arbitrary thresholds, and is thought to parallel the continuous nature of pathophysiology (Brown and Barlow, 2005). A dimensional approach also allowed us to examine ADHD symptoms and impairment separately.

7.5.4 Multi-method cognitive and EEG approach

Throughout this thesis, a combination of cognitive-performance, ERP, EEG activity and connectivity measures were used. Measures of cognitive performance provide global information on participants' speed and accuracy during cognitive tasks. The precise temporal resolution and direct measurement of brain activity with EEG further provide insights into sub-second stages of information processing underlying overt and covert cognitive processes. The analysis of ERP components employed in most studies (Chapters 2, 4, 5, 6) is a robust and well-validated approach to investigate, with millisecond resolution, differential information-processing stages in evoked brain responses to task stimuli (Banaschewski and Brandeis, 2007, Luck et al., 2011). More recent and advanced analytic approaches were also employed to examine event-related modulations of brain activity and connectivity. Time-frequency analyses examined changes in power and phase variability (Chapters 6), which provided fine-grained information beyond evoked brain activity captured by ERPs. Of particular relevance for ADHD and BD, which have both been associated with increased response variability, the examination of inter-trial coherence (ITC) in EEG phase (Chapter 6) provided an index of neural variability in the processing of a stimulus repeated over trials, which may parallel variability at the cognitive level (McLoughlin et al., 2014b, Groom et al., 2010a). Finally, while most EEG indices employed in this thesis have been measured at a single scalp location or a region where activity was maximal, as is common practice in ERP and time-frequency analyses, connectivity analyses examined the brain-wide interaction between brain activities from different scalp regions (Chapter 3). The use of network-based metrics allowed to examine brain network properties in the way brain connectivity differs between groups, with consistent results both for measures of local connectedness and of global connectivity.

7.5.5 Generalisability

The age ranges of the samples included in this thesis were restricted to adolescence (Chapters 2-4) and early or middle adulthood (Chapters 2-6). Considering that maturational effects on

cognitive and neurophysiological indices are well documented in previous studies (Liechti et al., 2013, Valko et al., 2009, Michels et al., 2013, Poil et al., 2014, Rommel et al., 2015), the results cannot be generalised to age groups outside those studied. Since the samples used in the first three chapters spanned both adolescence and young adulthood, age was controlled for in all analyses to account for age effects. Participants included in the last two chapters were all in early or middle adulthood, thus further studies are needed to compare ADHD and BD earlier or later in the lifespan. To understand how the association of cognitive-neurophysiological impairments with ADHD and BD may differ with development, replication of these studies at different developmental stages is required. With regard to generalisability across genders, the majority of participants in the samples for the studies in the first part of this thesis were males, thus providing limited information on the investigated impairments in females with ADHD. Conversely, the sample used for the last two thesis chapters was an all-female sample, in order to match groups on sex in this smaller-scale study. It remains unclear, however, if the results would generalise to adult men, warranting further investigation. In relation to IQ, participants with ADHD and unaffected siblings showed significantly lower IQ than control participants, as is typical for individuals with the disorder (Frazier et al., 2004) and reported in previous family studies (Rommelse et al., 2008c, Wood et al., 2011). This variable was directly examined in relation to cognitive-neurophysiological impairments in ADHD in the first part of this thesis, by performing analyses with and without controlling for IQ (Chapters 2 and 3) and including IQ into multivariate model-fitting analyses (Chapter 4). The sample for the ADHD and BD study was well matched on IQ, thus results may not be fully representative of more heterogeneous clinical populations. Yet, lower IQ scores relative to neurotypical individuals have been reported both in individuals with ADHD (Frazier et al., 2004) and individuals with BD (Joseph et al., 2008, Olvet et al., 2013). As such, whether the findings based on these groups generalise to more typical individuals with ADHD or BD remains to be tested in future studies of individuals with more characteristic IQ profiles.

7.5.6 Effects of medication

Potential effects of medication are difficult to control for in psychiatric research, especially when differences may exist in the type of prescribed medication to individuals with psychiatric conditions. In all studies included in this thesis, individuals with ADHD were asked to stop taking the medication they had been prescribed for the disorder 48 hours before the testing sessions. This is a standard procedure in cognitive and neurophysiological studies of ADHD (Cheung et al., 2016, McLoughlin et al., 2009). As such, the findings in individuals with ADHD reported in this

thesis cannot be attributed to short-term effects of ADHD medication on the investigated measures. However, long-term effects of ADHD medication use cannot be fully excluded. In Chapters 2 and 3, a comparable proportion of individuals in remitted and persistent ADHD groups were taking medication at follow-up. This potentially suggests that medication at the time of the assessments may not impact the differences in clinical or cognitive-EEG measures between ADHD remitters and persisters. Yet, information on previous use of medication between the childhood and follow-up assessments were not available in this study. As such, it cannot be determined whether the findings of these studies could be partly attributed to individual differences in long-term effects of ADHD medication.

In the studies described in the second part of this thesis, it was not possible, for ethical reasons, to ask participants to stop taking mood-stabilising, anti-psychotic or antidepressant medications. The effects of medication pose a particularly difficult challenge in cross-disorder studies where different groups are prescribed different drug treatments. Due to the limited number of participants in medication sub-groups, it was not possible to directly test the effect of medication on impairments in cognitive and EEG measures in ADHD and BD, which represents a limitation of the current study. However, previous studies suggest that medications may show positive effects (reducing differences from controls) or limited effects on cognitive-EEG measures (Anderer et al., 2002, Karaaslan et al., 2003, Galletly et al., 2005, Degabriele and Lagopoulos, 2017). As such, it seems unlikely that the group differences and impairments reported in individuals with ADHD or BD in the studies included in this thesis reflect confounding effects of medication.

7.5.7 Multiple testing

Due to the exploratory nature of the cognitive-electrophysiological investigations included in this thesis, multiple testing corrections were not applied in most analyses, in order to limit the chance of introducing type-two errors (false negatives). When applying multiple-testing corrections was deemed not appropriate, analyses were restricted to variables that were expected to be sensitive to impairments in ADHD or BD. For example, ERP analyses were limited to amplitude measures, and did not examine group differences on peak latencies, as most previous studies using the tasks included in this thesis found that alterations primarily involve amplitude differences (McLoughlin et al., 2010, McLoughlin et al., 2009). In the cross-disorder comparison study between ADHD and BD multiple testing corrections were further not applied to reduce false negatives, as this study was set up as a pilot investigation to identify potential

biomarkers to validate in larger-scale studies. Due to the exploratory nature of these analyses, future replication of the results will be important before drawing conclusions on shared and distinct alteration in ADHD and BD. In addition, in interpreting the results, emphasis was placed both on effects sizes and p-values of significance. Given the large number of variables included in the brain connectivity study (Chapter 3), which was higher than in the other more hypothesis-driven studies, false-discovery rate corrections for multiple testing were applied.

7.6 Future directions

7.6.1 Replication

As all the studies in this thesis are novel, replication of the findings in independent samples will be required, both using the same measures and using different measures capturing comparable cognitive and neurophysiological processes. The studies on cognitive, EEG activity and connectivity markers in individuals with remitted and persistent ADHD (Chapters 2 and 3) are the first of their kind using a performance monitoring task, and future studies are needed to confirm the results and conclusions. Similarly, the study on the aetiological structure of cognitive-neurophysiological impairments is ADHD (Chapter 4) is the first conducted in a clinical sample of adolescents and young adults, as well as using both cognitive-performance and ERP measures; thus replication is warranted. Performing comparable analyses on a twin sample would further help establish to what extent the identified familial factors reflect largely shared genetic influences or also shared environmental influences.

Replication in large samples will be especially important for the studies on ADHD and BD (Chapters 5 and 6), which included a relatively small sample compared to the studies in the previous chapters. Despite the modest sample size, these studies represent some of the first empirical data comparing adults with ADHD and adults with BD on ERP and brain-oscillatory markers of attentional and inhibitory processes. Although initial internal replication emerged (e.g., for the CNV and attentional P3 components, comparable results were obtained in both chapters), future studies with larger samples and including individuals of both sexes are needed to confirm and generalise these findings.

7.6.2 Examining other definitions of ADHD

In all chapters included in this thesis, ADHD was defined based on diagnostic criteria from the DSM-IV (APA, 2000), which was the DSM version in use at the time of setting up the data collection for the samples included in this thesis. Future studies should aim to replicate these findings using the current DSM-5 criteria for ADHD. In addition, clinical guidelines recommend different informant to ascertain ADHD symptoms and impairments at different stages of development; i.e., parent-report in childhood and adolescence (Taylor et al., 2004) and self-report in adulthood (Kooij et al., 2010). Given the wide age range (11-27 years) of the ADHD and control sibling-pair sample (Chapters 2, 3 and 4), consistency in reports to establish ADHD diagnosis was achieved by using parent-report symptoms and impairments in all participants. Parent-report measures were chosen over self-report measures, as the latter showed limited agreement with objective markers (cognitive-performance and EEG measures) of ADHD remission and persistence in this sample (Du Rietz et al., 2016). Specifically, the same cognitive-EEG measures that distinguished between ADHD remitters and persisters using parent-reported ADHD outcome (Cheung et al., 2016) distinguished poorly between ADHD groups based on self-report (Du Rietz et al., 2016). Future studies should further investigate the reliability and value of different informant accounts, and how these results may vary using different informants. ADHD diagnosis in Chapters 5 and 6 was based on self-report ADHD symptoms and impairment, as all participants in this cross-disorder study were adults (age range: 20-52 years), and self-report is also commonly used for BD in adulthood. Future studies may, however, benefit from the collection of clinical information also from co-informants.

7.6.3 Developmental associations between ADHD and cognitive impairments

Chapter 4 investigated the aetiological structure of cognitive and neurophysiological impairments in ADHD in adolescence and young adults, using both cognitive-performance and EEG data. Although data used in this analysis represent a follow-up investigation in a subsample of a study investigating cognitive impairments in ADHD in childhood (Kuntsi et al., 2010), the cognitive batteries used in the two assessments were partly different, and EEG data was not available in childhood. Given the strong emphasis on neurophysiological markers in this thesis, analyses were restricted to the follow-up assessment where both cognitive and EEG data were available. Future analyses could examine the aetiology of the longitudinal association between ADHD and cognitive measures available at both time points (IQ, DSF, DSB, MRT and RTV from the Fast task). Previous analyses at each time point have shown evidence of substantial familial

risk factors underlying the association between cognitive impairments and ADHD (Kuntsi et al., 2010, Chapter 4). Longitudinal analyses will allow to examine the extent to which familial and non-familial aetiological factors explain the developmental relationships between ADHD and cognitive measures. The sibling-pair nature of this sample will further enable to examine the contribution of familial and non-familial aetiological factors to the developmental stability and change in these cognitive measures and ADHD symptoms from childhood to young adulthood.

7.6.4 Source-based and single-trial EEG analyses

The neurophysiological indices used in this thesis were extracted with a variety of traditional and more advanced EEG analytic approaches applied to scalp-level data from EEG channels, in line with most previous EEG studies in ADHD (Albrecht et al., 2008, Cheung et al., 2016, McLoughlin et al., 2010, Groom et al., 2010b). Analyses of channel activities usually rely on averaging of EEG signals to enhance the signal-to-noise ratio, in order to obtain meaningful waveforms, connectivity matrices and brain-oscillatory indices. Due to the relatively poor signal-to-noise ratio of scalp-EEG activity, analysis of EEG signals on a single-trials basis is difficult with EEG scalp data. In addition, despite EEG provides excellent temporal resolution, EEG scalp distributions derived from traditional EEG methods result from a mixing of several overlapping brain sources simultaneously projecting at the scalp (Makeig et al., 1997, Makeig et al., 2004a). As such, these traditional methods do not allow to precisely localise neural processes in the brain.

Advances in EEG methodologies provide an alternative to the analysis of channel data, by using statistical and computational approaches to derive and separate the activity of underlying brain sources with enhanced spatial resolution (McLoughlin et al., 2014a, Loo and Makeig, 2012, Makeig et al., 2004a). One such analysis technique is independent-component analysis (ICA), which allows to decompose the mixing of brain sources and isolate the activity of temporally independent individual sources of EEG activity, thus improving signal-to-noise ratio in detecting brain activity (Makeig et al., 1997, Makeig et al., 2004a). Although investigators have only recently begun to apply these approaches to data from individuals with psychiatric or neurodevelopmental disorders, it has been suggested that analysing source activity may potentially capture impairments in clinical conditions more in detail (Grin-Yatsenko et al., 2010, Loo et al., 2015, McLoughlin et al., 2014b, McLoughlin et al., 2014a). These methods may, in turn, allow further characterisation of developmental outcomes of ADHD or delineation between ADHD and BD. For example, the improved signal-to-noise ratio gained with source-

based analyses may allow the examination of EEG signals on a trial-by-trial analyses, which would be particularly valuable to study ADHD and BD, as individuals with either disorder are characterised by high intra-individuals variability in cognitive processes (Kuntsi et al., 2013, Bora et al., 2006). It would be therefore useful to examine this variability at the neural level in future studies, linking variability at the neural level to variability at the cognitive level with single-trial analyses. Finally, these source-based methods allow more precise localisation of brain activity in anatomical brain regions, bridging the gap in spatial resolution between EEG and other neuroimaging techniques such as fMRI (McLoughlin et al., 2014a, Loo and Makeig, 2012, Makeig et al., 2004a). Future studies could further perform brain connectivity analyses on these source activities, rather than on scalp-based data, which would enable the investigation of functional connectivity between more localised functional networks without contamination of volume conduction (Loo et al., 2015, Coben et al., 2014). The examination of the dynamic formation of functional networks between brain sources during cognitive processes could also be examined (Lenartowicz et al., 2014).

7.6.5 Persistence and remission of ADHD in middle and late adulthood

The follow-up assessment in the sample used for the first part of this thesis was in adolescence and early adulthood. Since about half of the participants were still adolescents, not all participants may have remitted by the follow-up assessment, but may still remit later in development. Although longitudinal studies of cognitive and neurophysiological processes in ADHD samples are limited to date, a small-scale longitudinal ERP study suggests that there may be a maturational lag in the development of neurophysiological inhibitory control (NoGo-P3), but not for attentional processes (Cue-P3), in individuals with ADHD (Doehnert et al., 2010). Further evidence also indicates that longitudinal studies using structural MRI show that prefrontal brain areas continue to develop until young adulthood (Shaw et al., 2006). Therefore, the possibility remains that the lack of differences between ADHD persisters and remitters in largely prefrontally-mediated executive functions could be due to the young age at follow-up, as these processes may continue to develop, and potentially improve in remitters, into adulthood. As such, a further future direction for research should be to carry out additional follow-up assessments of the ADHD and control sibling-pair sample in middle and late adulthood.

Extending the investigation to a new follow-up with cognitive and EEG assessments when all the participants have reached adulthood would provide the new data on markers of remission and

enduring deficits, as well as of the developmental changes in clinical, cognitive and neurophysiological profiles from childhood to adulthood. In particular, identical EEG measures between follow-up assessments would allow to examine differences between ADHD remitted and persistent groups while controlling for baseline assessments. Since data from the arrow flanker task were not available in the childhood assessments, these analyses on data from a further follow-up with identical measures would be needed to rule out the possibility that differences in the measured identified as markers of remission between ADHD remitters and persisters could not be already explained by subtle differences between the two groups at baseline assessments, although all individuals were affected in childhood.

7.7 Overall conclusions

Overall, by using a combination of cognitive, neurophysiological, developmental, and sibling-modelling approaches, the work presented in this thesis furthers our understanding of impairments in cognitive and brain function in adolescents and adults with ADHD. This thesis focused, in particular, on the developmental and aetiological pathways to ADHD outcomes, and on the specificity or overlap with BD. These findings indicate that certain cognitive-neurophysiological impairments are sensitive to different developmental outcomes of the disorder, map onto multiple familial factors, and largely overlap with alterations observed also in BD. The identification of cognitive and neurophysiological measures linked to the varied clinical outcomes of ADHD provides new evidence of neural markers that may underlie remission of symptoms and impairments, but also of neural alterations that may not be sensitive to developmental outcomes of remission or persistence. By examining the aetiological structure of cognitive and neurophysiological impairments in ADHD, this thesis further provides new insights into the relationship and separation between these impairments in ADHD in adolescence and early adulthood, both at the phenotypic and aetiological level. Finally, the cross-disorder examination of ADHD in comparison with BD provides novel evidence of widespread overlap in cognitive and neurophysiological impairments, but also of few distinct alterations in ADHD and BD.

The findings and implications discussed in this final chapter highlight the value of combining multiple methodological approaches and levels of analysis from aetiological factors, neural mechanisms, cognitive processes and behavioural outcomes to gain a deeper understanding of the pathways to ADHD. The temporal precision of EEG provided sub-second temporal resolution

to characterise impairments in various stages of information processing and brain function. The use of multiple EEG analysis approaches further allowed the investigation of various aspects of neural processes, including brain activity, variability and connectivity. Future longitudinal studies integrating repeated assessments of cognitive measures and neurophysiological indices at various developmental stages will be particularly useful in further characterising the developmental trajectories of the various separable processes in relation to the course of ADHD into adulthood. Further research efforts should also aim to continue examining the neurobiological mechanisms that may be specific to ADHD or shared with other disorders, such as BD. The neurophysiological measures able to discriminate between ADHD and BD may be candidate biomarkers which, if replicated in larger studies, could be examined and validated in clinical settings to aid in the distinction between the two disorders when this is unclear from clinical profiles.

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Appendix A - Chapter 2 supplementary material

8.1 Further details on the task

The version of Eriksen flanker task used in this study consisted of 10 blocks of 40 trials where congruent versus incongruent conditions and the direction of responses (left versus right) were counter-balanced and randomized. Participants were seated on an adjustable chair in an acoustically shielded, video-monitored room. Two practice blocks were administered before the task blocks and task comprehension was ascertained prior to task performance. On congruent trials, flanker and target arrowheads pointed in the same direction; on incongruent trials, they pointed in opposite directions. Flankers were presented every 1650 ms (inter-trial interval (ITI), therefore an inter-block interval (IBI) was 1400 ms). ITI and IBI were fixed. After each block, feedback was presented on screen to emphasize both speed and accuracy, in order to encourage participants to make enough errors to enable analysis of ERN/Pe components, and enough correct responses for analysis of the N2. Where participants made > 10% errors on congruent or > 40% errors on incongruent trials, they were instructed to slow down. Where participants made < 10% errors on congruent or < 40% errors on incongruent trials, they were instructed to perform faster. If neither rule applied, feedback informed participants to continue the same way. The task was run during a 1.5-hour recording session between two other tasks not reported here: preceded by the cued continuous performance test (CPT-OX) and followed by the Fast task (see (Cheung et al., 2016) for details). Breaks of at least 5 minutes were given in between tasks. Where necessary, participants were told to minimize movement or blinking.

8.2 Comparison between peak-to-peak and peak-to-baseline ERN

In the present study, the ERN was measured with reference to the previous preceding positive peak (the PNe, occurring between -100 and 50ms), consistently with several previous studies in the literature (Falkenstein et al., 2000, Falkenstein et al., 2001, Frank et al., 2005, Gentsch et al., 2009, Kopp et al., 1996, Nieuwenhuis et al., 2001, Nieuwenhuis et al., 2003). In these studies, this measurement of the ERN has proven useful to account for individual variability in amplitude range and to reduce latent low-frequency noise. The peak-to-peak ERN measure is also a robust index of early error processing, which has been shown to delineate ADHD from controls in

independent samples using this version of the Eriksen flanker task (Albrecht et al., 2008, Albrecht et al., 2010, McLoughlin et al., 2009). Since some previous studies on ADHD samples have instead measured the ERN as a peak-to-baseline measure (Groom et al., 2010, O'Connell et al., 2009, Wiersema et al., 2009), we also investigated the differences between ADHD remitters, persisters and controls on this peak-to-baseline measure and on the PNe directly, for completeness and to allow comparison with previous results.

For the peak-to-baseline ERN we found significant overall group differences ($p=.05$) and ADHD persisters vs. controls difference ($p<.01$), but ADHD remitters did not significantly differ from either persisters ($p=.47$) or controls ($p=.34$). We did not find any group differences on the PNe (overall group effect: $p=.18$; ADHD remitters vs. persisters: $p=.27$; ADHD remitters vs. controls: $p=.69$; ADHD persisters vs. controls: $p=.14$).

Considering these results, the peak-to-baseline ERN may be less sensitive to ADHD remission/persistence compared to the peak-to-peak ERN. Of note, the analysis of PNe alone showed no group differences on this measure, thus the inclusion of this earlier peak in the peak-to-peak measure of the ERN did not explain the group differences on the peak-to-peak ERN, which reflect the voltage change from the PNe to the negative ERN.

Table S2.1. Pearson correlations between cognitive and ERP measures and age, divided by group

	Pearson *r* with age		
	Controls	**ADHD-R**	**ADHD-P**
Congruent errors	0.01	-0.19	-0.23*
Incongruent errors	-0.14†	-0.27	-0.29*
Congruent MRT (ms)	0.13	0.02	0.17
Incongruent MRT (ms)	-0.15†	-0.02	-0.20†
Congruent RTV (ms)	0.18*	0.07	0.23*
Incongruent RTV (ms)	0.25**	0.05	0.18
N2 at Fz (μV)	-0.42**	-0.41†	-0.39*
N2 at FCz (μV)	-0.28**	-0.03	-0.15
ERN (peak) at FCz (μV)	-0.25**	0.19	-0.09
ERN (peak-to-peak) at FCz (μV)	-0.12	0.10	0.07
Pe at CPz (μV)	-0.36**	-0.46*	-0.25*

*Abbreviations: ADHD-R = ADHD remitters; ADHD-P = ADHD persisters; Congruent = congruent condition; Incongruent = incongruent condition; MRT = reaction time of correct response to targets; RTV = reaction time variability to targets (SD of reaction time). **p≤.01; *p≤.05; †p<.09.*

Table S2.2. Full results of random intercept linear models showing main effects of group, condition (congruency), site (for the N2 only), and interaction effects on cognitive-performance and ERP measures

	Group effect		**Congruency effect**		**Group-by-Congruency**		**Site effect**		**Group-by-Site**	
	z	**p**	**z**	**p**	**z**	**p**	**z**	**p**	**z**	**p**
Errors	7.95	<.01**	43.39	<.01**	-5.22	<.01**	-	-	-	-
MRT	0.16	.87	582.71	<.01**	2.91	<.01**	-	-	-	-
RTV	-10.24	<.01**	-90.07	<.01**	6.95	<.01**	-	-	-	-
N2	2.64	<0.01**	9.65	<.01**	-.33	.74	83.22	<0.01**	-3.36	<0.01**

Abbreviations: MRT = reaction time of correct response to targets; RTV = reaction time variability to targets (SD of reaction time).
*Data on performance measures were available for the full sample (87 ADHD-P, 23 ADHD-R and 169 controls); data on the N2 were available for 84 ADHD-P, 23 ADHD-R and 169 controls. Age was also included as a covariate and its effects not presented here for simplicity, but available on request. Only group effects were tested on the ERN and Pe, thus regression models (rather than random intercept linear models) were used and the full results are presented in Table 2.2 of Chapter 2. **p≤.01; *p≤.05; †p<.09.*

Table S2.3. Descriptive statistics and group comparison on cognitive-performance and ERP measures performed only on males

	ADHD-P	ADHD-R	Ctrl	Group Comparison					
Performance	**mean (SD)**	**mean (SD)**	**mean (SD)**	**p**	**ADHD-P vs Ctrl**		**ADHD-P vs ADHD-R**		**ADHD-R vs Ctrl**	
					d	**p**	**d**	**p**	**d**	**p**
Congruent errors	9.59 (13.570	4.00 (3.85)	4.01 (7.10)	<.01**	*.73*	<.01**	*.68*	.01**	.00	.97
Incongruent errors	57.96 (18.59)	56.22 (20.75)	50.66 (18.69)	<.01**	.46	<.01**	.09	.81	.35	.13
Congruent MRT (ms)	352.47 (62.91)	339.58 (38.99)	332.45 (33.08)	<.01**	.42	<.01**	.19	.43	.23	.32
Incongruent MRT (ms)	448.12 (59.19)	441.94 (33.44)	428.37 (41.89)	<.01**	.41	<.01**	.02	.95	.42	.02*
Congruent RTV (ms)	113.94 (70.72)	83.19 (28.22)	74.40 (19.75)	<.01**	**.99**	<.01**	*.53*	.01**	.43	.05*
Incongruent RTV (ms)	121.34 (86.84)	88.18 (32.91)	75.51 (22.99)	<.01**	**.97**	<.01**	.45	.05*	*.53*	.02*
ERPs	**mean (SD)**	**mean (SD)**	**mean (SD)**	**p**	**ADHD-P vs Ctrl**		**ADHD-P vs ADHD-R**		**ADHD-R vs Ctrl**	
					d	**p**	**d**	**p**	**d**	**p**
N2 at Fz (μV)	-7.33 (3.74)	-6.91 (3.61)	-6.50 (3.30)	.02*	.34	.10	.05	.64	.29	.05*
N2 at FCz (μV)	-5.91 (3.89)	-6.26 (3.57)	-7.04 (3.92)	.09†	.26	.11	.14	.30	.12	.85
ERN at FCz (peak-to-peak, μV)	-7.97 (3.38)	-9.64 (4.11)	-9.99 (4.12)	<.01**	**.52**	<.01**	.47	.09†	.06	.78
Pe at CPz (μV)	9.67 (4.14)	10.96 (4.06)	11,50 (4.45)	.02*	.41	.02*	.38	.11	.04	.91

Abbreviations: ADHD-P = ADHD persisters, ADHD-R = ADHD remitters, Ctrl = Control group, SD = standard deviation, p = regression model significant testing, d = Cohen's d effect size (0.2 small, 0.5 medium and 0.8 large), Congruent = congruent condition, Incongruent = incongruent condition, MRT = reaction time of correct response to targets, RTV = reaction time variability to targets (i.e., SD of reaction time).
Notes: Data on performance measures and N2 were available for 72 ADHD-P, 23 ADHD-R and 128 controls; data on the ERN and Pe were available for 69 ADHD-P, 19 ADHD-R and 111 controls. Age was included as a covariate in all analyses and its effects are not presented here for simplicity, but available on request.
*Bold denotes a large effect size, italics denotes a medium effect size. **p≤.01; *p≤.05; †p≤.09.*

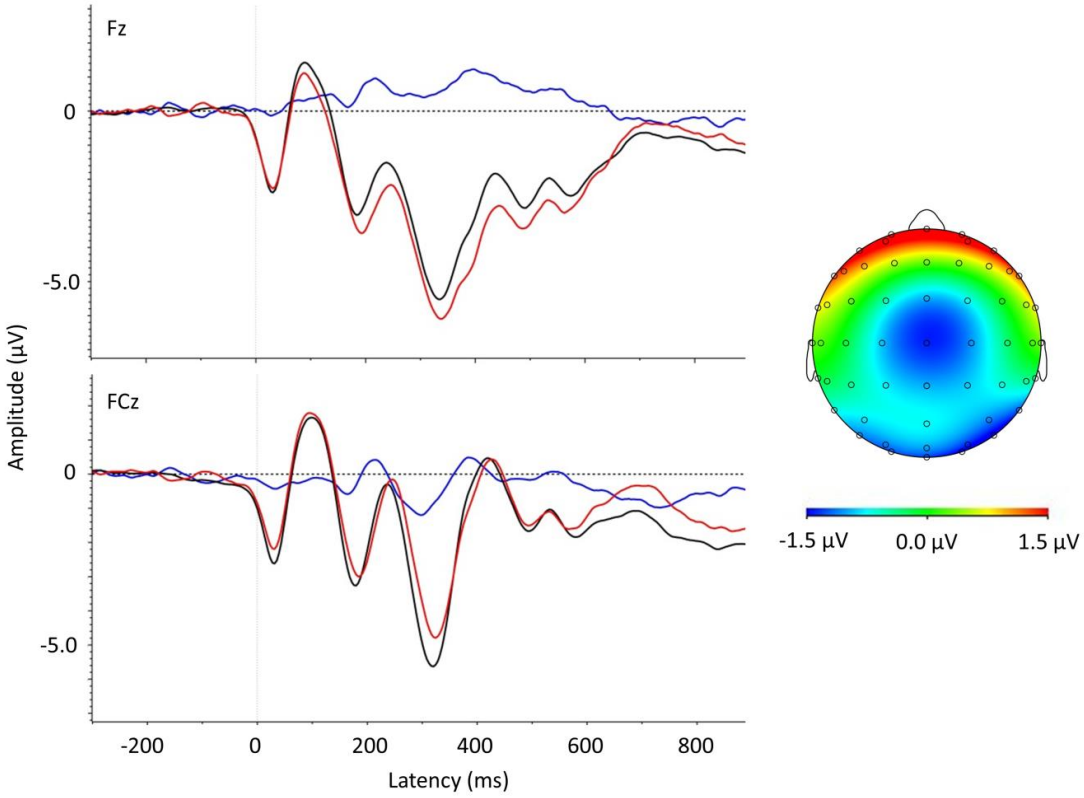

Figure S2.1. *Difference wave (in blue) showing the difference between ADHD persisters (ADHD-P, in red) and control participants (Controls, in black) in grand average stimulus-locked ERPs of the N2 at Fz and FCz electrodes between 250 and 450 ms after incongruent stimuli where a correct response was made, with t-map.*
Note: Topographical differences between ADHD persisters and controls can be observed here, which likely led to an enhanced N2 in persisters at Fz but with a trend for reduction at FCz. This is indicated in the grand average ERP showing the difference wave (in blue, ADHD persisters minus controls), which appears in the positive region of the graph at Fz (corresponding to the positive frontal difference in yellow-red in the t-map) and in the negative region of the graph at FCz (corresponding to the negative central difference in blue in the t-map).

8.3 Appendix A - References

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Appendix B - Chapter 3 supplementary material

9.1 Further details on the task

The version of Eriksen flanker task used in this study consisted of 10 blocks of 40 trials where congruent vs incongruent conditions and the direction of responses (left vs right) were counter-balanced and randomised. Participants were seated on an adjustable chair in an acoustically shielded, video-monitored room. Two practice blocks were administered before the task blocks and task comprehension was ascertained prior to task performance. On congruent trials, flanker and target arrowheads pointed in the same direction; on incongruent trials, they pointed in opposite directions. Flankers were presented every 1650 ms (inter-trial interval [ITI], therefore an inter-block interval [IBI] was 1400 ms). ITI and IBI were fixed. After each block, feedback was presented on screen to emphasise both speed and accuracy, to encourage participants to make enough errors to enable analysis of trials with incorrect responses, and enough correct responses for analysis of correct responses. Where participants made >10% errors on congruent or >40% errors on incongruent trials, they were instructed to slow down. Where participants made <10% errors on congruent or <40% errors on incongruent trials, they were instructed to perform faster. If neither rule applied, feedback informed participants to continue the same way. The task was run during a 1.5-hour recording session between two other tasks: preceded by a continuous performance test (CPT-OX) and followed by the Fast task (see Chapter 4). Breaks of at least 5 minutes were given in between tasks. When necessary, participants were told to minimise movement or blinking.

9.2 EEG connectivity and imaginary coherence

Several challenges exist when measuring functional brain connectivity from EEG recordings (Siegel et al., 2012). The phenomenon of volume conduction refers to the near-instantaneous spreading of electrical potential from brain sources throughout the brain volume, skull and scalp (Onton and Makeig, 2006, Lopes da Silva, 2004, Nunez et al., 1997). At the scalp level, artefacts due to volume conduction mean that the activity of a same source may be measured at multiple distant scalp sites with near-zero phase delays (Onton and Makeig, 2006, Makeig et al., 2004). This can substantially limit the ability to measure functional associations between brain signals

from different scalp channels. One effective way to capture connectivity between brain regions using scalp-level signals is to measures their non-instantaneous associations, which are phase-lagged (i.e., phase-shifted) and may thus not arise from artefacts of volume conduction. One of the main measures to assess phase-lagged connectivity is the imaginary part of the measure coherence (iCoh) (Nolte et al., 2004). In the present study, iCoh values were calculated between pairs of brain signals from every EEG channel in order to obtain a measure of functional association between brain signals without contamination of volume conduction (Nunez et al., 1997). The phase coherence values between EEG signals were estimated by calculating their cross-spectrum for each time point with Fast Fourier Transforms using the "newcrossf" function in the EEGLAB toolbox (Delorme and Makeig, 2004) and the BioNeCt toolbox (https://sites.google.com/site/bionectweb/home; Coben et al., 2017) for Matlab. The imaginary part of the complex number phase coherence between two signals of same frequency was then isolated (Nolte et al., 2004). iCoh is measured in a scale between 0 and 1. When a zero-phase relationship exists between two signals, possibly due to volume conduction artefacts, iCoh is equal to 0. Instead, if two signals are phase lagged, this will result in a value of iCoh greater than 0 (Nolte et al., 2004).

9.3 Graph-theoretical metrics

When EEG signals are measured with high-density EEG recordings, performing a large number of statistical tests on the functional interactions between all pairs of electrodes carries problems of multiple comparisons. By applying network-based approaches, such as graph-theoretical metrics, it is possible to derive global network-based measures that can describe functional associations in terms of network properties and summarise information from multiple functional interactions between electrode pairs (Siegel et al., 2012, Bullmore and Sporns, 2009, Sporns, 2013). Graph theory is based on mathematical algorithms able to quantify the relationships ("edges") between brain signals from EEG channels, representing the "nodes" of a network. Here, a graph-theory approach was applied on iCoh values using undirected weighted graphs. A weighted graph is defined by a symmetric matrix of functional association values between 0 and 1, which shows the strengths of the connections between the corresponding nodes (EEG channels). In contrast to binary graphs, where connections are measured as present or absent, weighted graphs have been shown to preserve essential information of a network structure (Ahmadlou et al., 2012, Bullmore and Sporns, 2009, Barrat et al., 2004). Graphs were undirected, as the directionality of connections (i.e., effective connectivity) was not examined.

9.4 Analyses applying multiple-testing corrections

Given the large number of hypotheses tested, sensitivity analyses applied multiple-testing corrections with false discovery rate (FDR) on post-hoc tests with the "multproc" package in Stata, using the Simes method, which identifies those tests that remain significant (Simes, 1986). Multiple-testing corrections (controlling the FDR at 15%) on post-hoc group comparisons (separately for ADHD persisters vs controls, ADHD remitters vs controls, ADHD persisters vs remitters) showed that all significant differences between controls and ADHD remitters, and between controls and ADHD persisters remained significant. The only previously significant difference between ADHD persisters and remitters (in beta diameter) was no longer significant when correcting for multiple testing. All significant group differences on measures of pre-stimulus/post-stimulus change remained significant after correcting for multiple testing. Similarly, the statistically significant associations that emerged between a few connectivity measures and ADHD impairment were no longer significant when applying multiple-testing corrections.

9.5 Analyses on the male-only sample

The majority of individuals in our sample (80%) were males. Since groups were not fully matched on sex (Table 3.1), analyses were repeated with females (15 ADHD persisters, 41 controls) removed. Results were largely unchanged when rerunning analyses on the male-only sample (Table S3.3-S3.4). Only a few tests that were significant in the full sample on connectivity in the theta band became trend-level effects (p=0.05-0.10) in males only: the comparison between ADHD persisters and controls in pre-stimulus global efficiency in correct responses, and the comparison between ADHD remitters and controls in pre-stimulus diameter in correct responses and in post-stimulus average clustering coefficient, global efficiency and iCoh in error responses (Table S3.3). When repeating the analyses of within- and between-group change between time windows, differences between ADHD persisters and controls on the change between time windows in average clustering coefficient, global efficiency and mean iCoh during error trials, as well as between ADHD remitters and controls in theta diameter in correct trials and in alpha path length in correct trials, were no longer significant (Table S3.4).

9.6 Analyses covarying for IQ

ADHD persisters in this sample had a lower IQ than ADHD remitters and controls (Cheung et al., 2016), and childhood IQ predicted ADHD outcome at follow-up (Cheung et al., 2015). To examine whether IQ contributes to the differences between groups in brain connectivity, all analyses were re-run controlling for IQ. Results of group comparisons in the pre-stimulus and post-stimulus windows for correct and error responses remained the same when controlling for IQ (Table S3.5), with the only exceptions being that the comparisons between ADHD remitters and controls in alpha pre-stimulus global efficiency and alpha diameter in correct trials became significant (while they were at trend-level in the main analyses). When repeating the analyses of within- and between-group change between time windows covarying for IQ, differences between ADHD persisters and controls on the change between time windows in theta average clustering coefficient, global efficiency and mean iCoh during error trials, and in alpha global efficiency, path length and mean iCoh during error trials were no longer significant (Table S3.6).

When controlling for IQ in dimensional analyses, the results on the association between connectivity measures and DIVA ADHD symptoms (revealing no significant associations in the main analyses) remained unchanged. The statistically significant associations of impairment with post-stimulus global efficiency in the alpha band and pre-stimulus path length in the beta band in correct trials were no longer significant (at trend-level) when controlling for IQ, while the non-significant (trend-level) associations of impairment with pre-stimulus average clustering coefficient, global efficiency, path length and mean iCoh in the beta band in incorrect trials became significant (Table S3.7).

9.7 Analyses of connectivity within and between cortical regions

In addition to whole-brain connectivity analysis, we also examined patterns of local brain connectivity within cortical regions. Local connectivity was quantified with mean iCoh values between groups of electrodes. First, we computed mean iCoh within anterior (AF3, AF4, Fz, F1, F2, F3, F4, F5, F6, F7, F8, AF7, AF8), central (Cz, C1, C2, C3, C4, C5, C6, FCz, FC1, FC2, FC3, FC4, FC5, FC6, CPz, CP1, CP2, CP3, CP4, CP5, CP6), and posterior (Pz, P3, P4, P7, P8, PO7, PO8, PO3, PO4, POz, Oz, O1, O2) scalp regions. Secondly, we analysed connectivity within left (AF3, AF7, F1, F3, F5, F7, FC1, FC3, FC5, FT7, FT9, C1, C3, C5, T7, CP1, CP3, CP5, TP7, TP9, P3, P7, PO3, PO7,

PO9, O1) and right (AF4, AF8, F2, F4, F6, F8, FC2, FC4, FC6, FT8, FT10, C2, C4, C6, T8, CP2, CP4, CP6, TP8, TP10, P4, P8, PO4, PO8, PO10, O2) hemispheres (Figure S3.1). Both groups of analyses focused on correctly-responded trials only, where group differences where maximal. For the analysis of connectivity within each local region, random intercept linear models tested for main effects of group (ADHD persisters vs ADHD remitters vs controls), time window (pre-stimulus vs post-stimulus) and region (anterior vs central vs posterior region; left vs right hemisphere), and three-way group-by-window-by-region interactions on mean iCoh in the theta, alpha and beta bands separately. For the analysis of connectivity between anterior/central/posterior regions, random intercept linear models tested for main effects of group (ADHD persisters vs ADHD remitters vs controls), time window (pre-stimulus vs post-stimulus) and region (anterio-central vs anterio-posterior vs centro-posterior connectivity), and for three-way group-by-window-by-region interactions on mean iCoh between each of these regions in the theta, alpha and beta bands separately. Finally, for the analysis of connectivity between right and left hemispheres, random intercept linear models tested for main effects of group (ADHD persisters vs ADHD remitters vs controls) and time window (pre-stimulus vs post-stimulus), and for two-way group-by-window interactions on mean iCoh measured between the two hemispheres in the theta, alpha and beta bands separately.

For iCoh within anterior/central/posterior cortical regions, the three-way group-by-window-by-region and two-way group-by-region interactions were not significant for theta, alpha or beta (all $p>0.23$). These results indicate that the pattern of group differences did not vary in the three local regions. For beta, the two-way group-by-window interaction was further not significant ($p=0.50$), indicating that the group differences did not vary in the two time windows, in line with the whole-brain analysis. After removing these non-significant interactions, results of analyses on group differences in local connectivity within cortical regions were consistent with those on whole-brain connectivity. Specifically, post-hoc group comparisons showed that, for theta and alpha bands in the pre-stimulus window, ADHD persisters had significantly greater values of iCoh than controls ($p<0.02$) but did not differ from remitters ($p>0.21$). Relative to controls, remitters showed no differences in pre-stimulus theta ($p=0.39$) but significantly greater iCoh in pre-stimulus alpha ($p=0.04$). No group effects emerged in post-stimulus theta or alpha iCoh (all $p>0.10$). For beta, there were significant differences between ADHD persisters and controls ($p<0.001$) and between remitters and controls ($p=0.02$), with both ADHD groups showing greater iCoh than the control group, but no differences between persisters and remitters ($p=0.22$).

In the analyses of local connectivity within left/right hemispheres, the three-way group-by-window-by-hemisphere and two-way group-by-hemisphere interactions were not significant for theta, alpha or beta iCoh (all $p>0.60$). Group differences thus did not vary in the two hemispheres. For beta, the two-way group-by-window interaction was further not significant ($p=0.85$), indicating that the group differences did not vary in the two time windows, in line with the whole-brain analysis. After removing these non-significant interactions, results of analyses on group differences in local connectivity within left/right hemispheres were consistent with those on whole-brain connectivity. Post-hoc group comparisons showed, for theta and alpha iCoh in the pre-stimulus window, that ADHD persisters had significantly greater iCoh than controls ($p<0.02$) but did not differ from remitters ($p>0.29$). Relative to controls, remitters showed no differences in pre-stimulus theta ($p=0.55$) but differences approaching statistical significance emerged in pre-stimulus alpha ($p=0.05$), indicating greater iCoh in remitters than controls. No group effects emerged in post-stimulus theta or alpha iCoh (all $p>0.19$). For beta iCoh, there were significant differences between ADHD persisters and controls ($p<0.01$), between remitters and controls ($p=0.04$), indicating greater iCoh in both ADHD groups compared to controls, but no differences between persisters and remitters ($p=0.11$).

The analyses of local connectivity between anterior, central and posterior cortical regions showed that the three-way group-by-window-by-region and two-way group-by-region interactions were not significant for theta, alpha or beta iCoh (all $p>0.23$), indicating that the group differences at all frequency bands were comparable across anterio-central, anterio-posterior and centro-posterior connectivity. For beta iCoh, the two-way group-by-window interaction was further not significant ($p=0.50$), indicating that the group differences did not vary in the two time windows, in line with the whole-brain analysis. After removing these non-significant interactions, post-hoc comparisons showed the same pattern of differences between groups of whole-brain iCoh measures. In pre-stimulus theta and alpha, ADHD persisters showed significantly greater iCoh than controls (all $p<0.01$) but no differences from remitters (all $p>0.25$). Compared to controls, remitters showed no differences in theta iCoh ($p=0.44$) but significantly greater alpha iCoh ($p=0.01$). No group effects emerged in post-stimulus theta or alpha (all $p>0.48$). For beta iCoh, significant differences emerged between ADHD persisters and controls ($p<0.01$) and between remitters and controls ($p=0.02$), with both ADHD groups showing greater iCoh than controls, but not between persisters and remitters ($p=0.22$).

The analyses of connectivity between the left/right hemispheres showed that the two-way group-by-window interaction was significant for theta and alpha (all $p<0.02$), but not for beta

(0.92), in line with the analysis of whole-brain iCoh. Group differences on iCoh between the two hemispheres showed the same pattern of group differences yielded in the main analyses on whole-brain connectivity. Post-hoc group comparisons showed that, for theta and alpha iCoh in the pre-stimulus window, ADHD persisters showed significantly greater iCoh than controls ($p<0.05$) but did not differ from remitters ($p>0.39$). Relative to controls, remitters showed no differences in pre-stimulus theta ($p=0.40$) but differences approaching statistical significance emerged in pre-stimulus alpha ($p=0.05$), indicating greater iCoh in remitters than controls. No group effects emerged in post-stimulus theta or alpha (all $p>0.30$). For beta iCoh, there were significant differences between ADHD persisters and controls ($p<0.01$) and between remitters and controls ($p=0.02$), with both ADHD groups showing greater iCoh than controls, but no differences between persisters and remitters ($p=0.16$).

Table S3.1. Descriptive statistics (mean and standard deviation [SD]) for study variables divided by group

		Controls		ADHD-R		ADHD-P	
THETA		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Average clustering coefficient	*Pre, Corr*	0.058	0.011	0.061	0.009	0.066	0.014
	Pre, Err	0.091	0.019	0.085	0.016	0.091	0.018
	Post, Corr	0.097	0.021	0.092	0.015	0.095	0.022
	Post, Err	0.127	0.026	0.119	0.023	0.118	0.025
Global efficiency	*Pre, Corr*	0.063	0.015	0.065	0.010	0.070	0.016
	Pre, Err	0.096	0.023	0.089	0.017	0.095	0.020
	Post, Corr	0.109	0.026	0.100	0.020	0.105	0.027
	Post, Err	0.138	0.030	0.129	0.029	0.128	0.029
Path length	*Pre, Corr*	17.571	3.084	16.671	2.374	15.797	3.095
	Pre, Err	11.504	2.281	12.270	2.246	11.571	2.304
	Post, Corr	10.561	2.157	11.143	2.152	10.942	2.331
	Post, Err	8.132	1.630	8.659	1.762	8.810	1.898
Diameter	*Pre, Corr*	30.563	4.579	28.348	3.892	27.499	5.175
	Pre, Err	19.506	3.649	20.356	3.265	19.781	3.882
	Post, Corr	21.238	3.910	21.084	3.558	21.155	3.643
	Post, Err	15.307	2.904	15.729	2.714	16.192	3.139
Mean imaginary coherence	*Pre, Corr*	0.060	0.012	0.063	0.009	0.068	0.015
	Pre, Err	0.094	0.020	0.087	0.017	0.093	0.019
	Post, Corr	0.102	0.023	0.095	0.017	0.099	0.024
	Post, Err	0.132	0.027	0.124	0.025	0.122	0.026
ALPHA		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Average clustering coefficient	*Pre, Corr*	0.069	0.019	0.077	0.018	0.078	0.024
	Pre, Err	0.099	0.026	0.092	0.017	0.100	0.025

	Post, Corr	0.074	0.014	0.075	0.010	0.078	0.013
	Post, Err	0.104	0.017	0.095	0.014	0.100	0.017
	Pre, Corr	0.082	0.030	0.094	0.033	0.092	0.035
	Pre, Err	0.107	0.030	0.102	0.020	0.113	0.034
	Post, Corr	0.081	0.018	0.082	0.015	0.084	0.016
Global efficiency	*Post, Err*	0.111	0.019	0.100	0.015	0.106	0.018
	Pre, Corr	14.516	3.913	12.714	3.416	13.230	4.125
	Pre, Err	10.552	2.569	10.909	1.969	10.219	2.555
	Post, Corr	13.795	2.544	13.363	2.035	13.169	2.364
Path length	*Post, Err*	9.907	1.678	10.850	1.524	10.294	1.730
	Pre, Corr	27.304	5.210	24.828	5.459	24.927	5.713
	Pre, Err	18.570	3.770	19.499	3.374	18.534	3.988
	Post, Corr	25.133	3.944	24.676	3.278	23.665	3.940
Diameter	*Post, Err*	17.246	2.797	18.710	2.806	17.870	3.163
	Pre, Corr	0.073	0.022	0.081	0.021	0.082	0.027
	Pre, Err	0.101	0.024	0.096	0.017	0.105	0.027
	Post, Corr	0.077	0.015	0.078	0.011	0.081	0.014
Mean imaginary coherence	*Post, Err*	0.107	0.018	0.097	0.014	0.103	0.017
BETA		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	Pre, Corr	0.056	0.009	0.060	0.009	0.065	0.013
	Pre, Err	0.090	0.016	0.086	0.015	0.089	0.016
Average clustering	*Post, Corr*	0.057	0.008	0.061	0.009	0.064	0.014
coefficient	*Post, Err*	0.091	0.016	0.087	0.016	0.089	0.017
	Pre, Corr	0.059	0.010	0.062	0.009	0.067	0.014
	Pre, Err	0.092	0.016	0.088	0.016	0.091	0.017
Global efficiency	*Post, Corr*	0.058	0.008	0.063	0.009	0.066	0.015

	Post, Err	0.093	0.016	0.088	0.016	0.091	0.017
	Pre, Corr	18.294	2.502	17.130	2.342	16.292	2.892
	Pre, Err	11.648	2.054	12.183	2.151	11.783	2.028
	Post, Corr	18.216	2.161	17.010	2.265	16.374	2.927
Path length	*Post, Err*	11.515	2.039	12.139	2.264	11.852	2.053
	Pre, Corr	30.381	3.795	28.345	3.480	26.796	4.702
	Pre, Err	18.936	3.392	19.749	3.795	19.290	3.519
	Post, Corr	29.972	3.522	28.124	4.187	26.857	4.818
Diameter	*Post, Err*	18.726	3.295	19.627	3.623	19.506	3.549
	Pre, Corr	0.058	0.009	0.062	0.009	0.066	0.014
	Pre, Err	0.092	0.016	0.087	0.015	0.091	0.017
	Post, Corr	0.058	0.008	0.062	0.009	0.066	0.014
Mean imaginary coherence	*Post, Err*	0.092	0.016	0.088	0.016	0.090	0.017

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = correctly-responded trials; Ctrl = Control group; Err = incorrectly-responded trials; Pre = pre-stimulus time window; Post = post-stimulus time window. Data in correctly-responded trials were available for 83 ADHD persisters, 22 remitters, 166 controls; and in incorrectly-responded trials for 75 ADHD persisters, 20 remitters, 145 controls.

Table S3.2. Full results of random intercept linear models, showing p values for all main and interaction effects

THETA	Group	Window	Response	Group-by-Window	Group-by-Response	Group-by-Window-by-Response
Average clustering coefficient	0.258	<0.001***	<0.001***	0.001**	0.007**	0.688
Global efficiency	0.176	<0.001***	<0.001***	0.001**	0.045*	0.673
Path length	0.509	<0.001***	<0.001***	<0.001***	0.002**	0.018*
Diameter	0.307	<0.001***	<0.001***	0.001**	<0.001***	0.029*
Mean imaginary coherence	0.232	<0.001***	<0.001***	0.001**	0.014*	0.676
ALPHA	**Group**	**Window**	**Response**	**Group-by-Window**	**Group-by-Response**	**Group-by-Window-by-Response**
Average clustering coefficient	0.392	0.114	<0.001***	0.024*	<0.001***	0.853
Global efficiency	0.507	0.005**	<0.001***	0.002**	0.005**	0.721
Path length	0.305	0.507	<0.001***	0.022*	<0.001***	0.713
Diameter	0.158	<0.001***	<0.001***	0.106	<0.001***	0.642
Mean imaginary coherence	0.345	0.529	<0.001***	0.004**	<0.001***	0.794
BETA	**Group**	**Window**	**Response**	**Group-by-Window**	**Group-by-Response**	**Group-by-Window-by-Response**
Average clustering coefficient	0.038*	0.728	<0.001***	0.856	<0.001***	0.945
Global efficiency	0.047*	0.904	<0.001***	0.849	<0.001***	0.887
Path length	<0.001***	0.831	<0.001***	0.8305	<0.001***	0.989
Diameter	<0.001***	0.695	<0.001***	0.630	<0.001***	0.997
Mean imaginary coherence	0.047*	0.866	<0.001***	0.864	<0.001***	0.939

Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly-responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Age was included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 83 ADHD persisters, 22 remitters, 166 controls; and in incorrectly-responded trials for 75 ADHD persisters, 20 remitters, 145 controls.
**p<0.05; **p<0.01; ***p<0.001.*

Table S3.3. Group comparisons on graph-theory and imaginary coherence measures in male participants only

			Group comparison					
		Overall Group	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	
THETA		**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Pre, Corr*	0.052	0.019*	*0.55*	0.972	0.20	0.148	0.36
	Pre, Err	0.642	-	-	-	-	-	-
	Post, Corr	0.569	-	-	-	-	-	-
	Post, Err	0.014*	0.008**	0.28	0.058	0.26	0.878	0.03
Global efficiency	*Pre, Corr*	0.129	0.061	0.43	0.803	0.08	0.156	0.38
	Pre, Err	0.637	-	-	-	-	-	-
	Post, Corr	0. 398	-	-	-	-	-	-
	Post, Err	0.019*	0.012*	0.28	0.062	0.26	0.835	0.02
Path length	*Pre, Corr*	<0.001***	<0.001***	0.49	0.213	0.22	0.134	0.31
	Pre, Err	0.540	-	-	-	-	-	-
	Post, Corr	0.499	-	-	-	-	-	-
	Post, Err	0.376	-	-	-	-	-	-
Diameter	*Pre, Corr*	<0.001***	<0.001***	*0.54*	0.051	0.38	0.330	0.19
	Pre, Err	0.806	-	-	-	-	-	-
	Post, Corr	0.975	-	-	-	-	-	-
	Post, Err	0.578	-	-	-	-	-	-
Mean imaginary coherence	*Pre, Corr*	0.073	0.028*	*0.52*	0.957	0.16	0.151	0.37
	Pre, Err	0.654	-	-	-	-	-	-
	Post, Corr	0.511	-	-	-	-	-	-
	Post, Err	0.015*	0.009**	0.28	0.062	0.26	0.881	0.03
ALPHA		**Overall Group**	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	

		p	p	d	p	d	p	d
Average clustering coefficient	*Pre, Corr*	0.006**	0.001**	0.41	0.219	0.30	0.403	0.13
	Pre, Err	0.217	-	-	-	-	-	-
	Post, Corr	0.365	-	-	-	-	-	-
	Post, Err	0.130	-	-	-	-	-	-
Global efficiency	*Pre, Corr*	0.013*	0.004**	0.31	0.146	0.28	0.678	0.04
	Pre, Err	0.143	-	-	-	-	-	-
	Post, Corr	0.871	-	-	-	-	-	-
	Post, Err	0.283	-	-	-	-	-	-
Path length	*Pre, Corr*	0.004**	0.003**	0.28	0.027*	0.36	0.824	0.06
	Pre, Err	0.402	-	-	-	-	-	-
	Post, Corr	0.334	-	-	-	-	-	-
	Post, Err	0.426	-	-	-	-	-	-
Diameter	*Corr*	0.003**	0.001**	0.36	0.177	0.21	0.422	0.19
	Err	0.524	-	-	-	-	-	-
Mean imaginary coherence	*Pre, Corr*	0.004**	0.001**	0.38	0.174	0.28	0.425	0.11
	Pre, Err	0.126	-	-	-	-	-	-
	Post, Corr	0.548	-	-	-	-	-	-
	Post, Err	0.152	-	-	-	-	-	-
BETA		**Overall Group**	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	
		p	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	<0.001***	<0.001***	*0.69*	0.214	0.40	0.092	0.32
	Err	0.433	-	-	-	-	-	-
Global efficiency	*Corr*	<0.001***	<0.001***	*0.63*	0.291	0.33	0.092	0.31
	Err	0.431	-	-	-	-	-	-

Path length	*Corr*	<0.001***	<0.001***	*0.66*	0.027*	0.41	0.091	0.27
	Err	0.624	-	-	-	-	-	-
Diameter	*Corr*	<0.001***	<0.001***	*0.76*	0.024*	0.42	0.042*	0.32
	Err	0.588	-	-	-	-	-	-
Mean imaginary coherence	*Corr*	<0.001***	<0.001***	*0.67*	0.214	0.38	0.092	0.31
	Err	0.434	-	-	-	-	-	-

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = correctly-responded trials; Ctrl = Control group; d = Cohen's d effect size; Err = incorrectly-responded trials; p = random intercept linear model significant testing; Pre = pre-stimulus time window; Post = post-stimulus time window.

Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly-responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Since neither diameter in the alpha band, nor any measures in the beta band showed a significant group-by-window interaction, post-hoc effects of group were tested with correctly- and incorrectly-responded trials collapsed across pre-stimulus and post-stimulus time windows. Post-hoc comparisons between groups were run only on measures showing a significant overall group effect. Age was included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 68 ADHD persisters, 22 remitters, 125 controls; and in incorrectly-responded trials for 63 ADHD persisters, 20 remitters, 110 controls.

**p<0.05; **p<0.01; ***p<0.001. d≥0.20 = small effect size, d≥0.50 = medium effect (in italics).*

Table S3.4. Within- and between-group effects on measures of change between pre-stimulus and post-stimulus windows in graph-theory and imaginary coherence measures in male participants only

		Within-Group Change			Between-Group Change					
		Ctrl	ADHD-P	ADHD-R	ADHD-P vs Ctrl		ADHD-R vs Ctrl		ADHD-R vs ADHD-P	
THETA		**p**	**p**	**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	<0.001***	<0.001***	<0.001***	0.009*	0.37	0.025*	0.36	0.962	0.04
	Err	<0.001***	<0.001***	<0.001***	0.078	0.26	0.741	0.03	0.471	0.23
Global efficiency	*Corr*	<0.001***	<0.001***	<0.001***	0.018*	0.33	0.034*	0.34	0.929	0.03
	Err	<0.001***	<0.001***	<0.001***	0.125	0.22	0.801	0.01	0.801	0.22
Path length	*Corr*	<0.001***	<0.001***	<0.001***	<0.001***	*0.52*	0.025*	0.36	0.678	0.17
	Err	<0.001***	<0.001***	<0.001***	0.173	0.23	0.719	0.09	0.263	0.31
Diameter	*Corr*	<0.001***	<0.001***	<0.001***	<0.001***	*0.51*	0.061	0.33	0.491	0.20
	Err	<0.001***	<0.001***	<0.001***	0.200	0.20	0.755	0.12	0.256	0.30
Mean imaginary coherence	*Corr*	<0.001***	<0.001***	<0.001***	0.012*	0.35	0.027*	0.36	0.941	0.03
	Err	<0.001***	<0.001***	<0.001***	0.089	0.25	0.765	0.02	0.480	0.22
		Ctrl	**ADHD-P**	**ADHD-R**	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	
ALPHA		**p**	**p**	**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	0.031*	0.849	0.770	0.108	0.25	0.136	0.32	0.807	0.04
	Err	0.005**	0.990	0.604	0.283	0.26	0.117	0.17	0.537	0.12
Global efficiency	*Corr*	0.362	0.003**	0.050	0.108	0.27	0.203	0.32	0.848	0.04
	Err	0.218	0.039*	0.691	0.027*	0.38	0.133	0.25	0.397	0.16
Path length	*Corr*	0.083	0.930	0.323	0.275	0.15	0.091	0.34	0.372	0.19
	Err	0.024*	0.753	0.931	0.025*	0.38	0.087	0.32	0.700	0.09
Mean imaginary coherence	*Corr*	0.142	0.327	0.477	0.113	0.25	0.163	0.30	0.858	0.03
	Err	0.001**	0.581	0.793	0.021*	0.40	0.064	0.32	0.517	0.12

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = correctly-responded trials; Ctrl = Control group; d = Cohen's d effect size; Err = incorrectly-responded trials; p = random intercept linear model significance testing.

Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly-responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Post-hoc tests on within- and between-group effects of change were run only on measures showing a significant group-by-window interaction. Since in diameter in the alpha band and in all measures in the beta band this interaction was not significant, post-hoc within- and between-groups effects of change were not tested. Age was included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 68 ADHD persisters, 22 remitters, 125 controls; and in incorrectly-responded trials for 63 ADHD persisters, 20 remitters, 110 controls.

**p<0.05; **p<0.01; ***p<0.001. d≥0.20 = small effect size, d≥0.50 = medium effect (in italics).*

Table S3.5. Group comparisons on graph-theory and imaginary coherence measures covarying for IQ

			Group comparison					
		Overall Group	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	
THETA		**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Pre, Corr*	0.002**	<0.001***	0.46	0.690	0.20	0.086	0.25
	Pre, Err	0.501	-	-	-	-	-	-
	Post, Corr	0.649	-	-	-	-	-	-
	Post, Err	0.004**	0.003**	0.11	0.030**	0.22	0.759	0.12
Global efficiency	*Pre, Corr*	0.011*	0.003**	0.36	0.923	0.09	0.095	0.28
	Pre, Err	0.502	-	-	-	-	-	-
	Post, Corr	0.442	-	-	-	-	-	-
	Post, Err	0.005**	0.004**	0.12	0.032*	0.23	0.743	0.11
Path length	*Pre, Corr*	<0.001***	<0.001***	0.42	0.068	0.24	0.097	0.20
	Pre, Err	0.441	-	-	-	-	-	-
	Post, Corr	0.591	-	-	-	-	-	-
	Post, Err	0.320	-	-	-	-	-	-
Diameter	*Pre, Corr*	<0.001***	<0.001***	*0.50*	0.009**	0.43	0.298	0.09
	Pre, Err	0.735	-	-	-	-	-	-
	Post, Corr	0.848	-	-	-	-	-	-
	Post, Err	0.503	-	-	-	-	-	-
Mean imaginary coherence	*Pre, Corr*	0.004**	0.001**	0.43	0.762	0.17	0.087	0.26
	Pre, Err	0.505	-	-	-	-	-	-
	Post, Corr	0.594	-	-	-	-	-	-
	Post, Err	0.005**	0.004**	0.11	0.032*	0.22	0.764	0.11
ALPHA		**Overall Group**	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	

		p	p	d	p	d	p	d
Average clustering coefficient	*Pre, Corr*	0.001**	<0.001***	0.37	0.078	0.38	0.567	0.02
	Pre, Err	0.353	-	-	-	-	-	-
	Post, Corr	0.227	-	-	-	-	-	-
	Post, Err	0.090	-	-	-	-	-	-
Global efficiency	*Pre, Corr*	0.003**	0.001**	0.28	0.044*	0.37	0.954	0.07
	Pre, Err	0.247	-	-	-	-	-	-
	Post, Corr	0.685	-	-	-	-	-	-
	Post, Err	0.228	-	-	-	-	-	-
Path length	*Pre, Corr*	<0.001***	<0.001***	0.29	0.004**	0.45	0.626	0.15
	Pre, Err	0.506	-	-	-	-	-	-
	Post, Corr	0.117	-	-	-	-	-	-
	Post, Err	0.355	-	-	-	-	-	-
Diameter	*Corr*	<0.001***	<0.001***	0.36	0.036*	0.28	0.497	0.10
	Err	0.581	-	-	-	-	-	-
Mean imaginary coherence	*Pre, Corr*	0.001**	<0.001***	0.34	0.058	0.36	0.608	<0.01
	Pre, Err	0.250	-	-	-	-	-	-
	Post, Corr	0.350	-	-	-	-	-	-
	Post, Err	0.114	-	-	-	-	-	-
BETA		**Overall Group**	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	
		p	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	<0.001***	<0.001***	*0.57*	0.073	0.39	0.075	0.21
	Err	0.254	-	-	-	-	-	-
Global efficiency	*Corr*	<0.001***	<0.001***	*0.53*	0.108	0.33	0.075	0.22
	Err	0.267	-	-	-	-	-	-

Path length	*Corr*	<0.001***	<0.001***	*0.56*	0.003**	0.42	0.082	0.16
	Err	0.432	-	-	-	-	-	-
Diameter	*Corr*	<0.001***	<0.001***	*0.61*	0.003**	0.43	0.042*	0.20
	Err	0.299	-	-	-	-	-	-
Mean imaginary coherence	*Corr*	<0.001***	<0.001***	*0.56*	0.080	0.38	0.074	0.21
	Err	0.261	-	-	-	-	-	-

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = correctly-responded trials; Ctrl = Control group; d = Cohen's d effect size; Err = incorrectly-responded trials; p = random intercept linear model significance testing; Pre = pre-stimulus time window; Post = post-stimulus time window.

Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly-responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Since neither diameter in the alpha band nor any measures in the beta band showed a significant group-by-window interaction, post-hoc effects of group were tested for with correctly- and incorrectly-responded trials collapsed across pre-stimulus and post-stimulus time windows. Post-hoc comparisons between groups were run only on measures showing a significant overall group effect. Age was included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 83 ADHD persisters, 22 remitters, 166 controls; and in incorrectly-responded trials for 75 ADHD persisters, 20 remitters, 145 controls.

**p<0.05; **p<0.01; ***p<0.001. d≥0.20 = small effect size, d≥0.50 = medium effect (in italics).*

Table S3.6. Within- and between-group effects on measures of change between pre-stimulus and post-stimulus windows in graph-theory and imaginary coherence measures covarying for IQ

		Within-Group Change			Between-Group Change					
		Ctrl	ADHD-R	ADHD-P	ADHD-P vs Ctrl		ADHD-R vs Ctrl		ADHD-R vs ADHD-P	
THETA		**p**	**p**	**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	<0.001***	<0.001***	<0.001***	0.021*	0.21	0.022*	0.32	0.747	0.07
	Err	<0.001***	<0.001***	<0.001***	0.120	0.14	0.770	<0.01	0.557	0.14
Global efficiency	*Corr*	<0.001***	<0.001***	<0.001***	0.041*	0.19	0.033*	0.30	0.718	0.08
	Err	<0.001***	<0.001***	<0.001***	0.161	0.13	0.793	<0.01	0.589	0.13
Path length	*Corr*	<0.001***	<0.001***	<0.001***	<0.001***	0.39	0.025*	0.35	0.678	0.06
	Err	<0.001***	<0.001***	<0.001***	0.173	0.17	0.719	0.14	0.263	0.29
Diameter	*Corr*	<0.001***	<0.001***	<0.001***	<0.001***	0.43	0.021*	0.36	0.567	0.09
	Err	<0.001***	<0.001***	<0.001***	0.273	0.12	0.630	0.17	0.238	0.28
Mean imaginary coherence	*Corr*	<0.001***	<0.001***	<0.001***	0.027*	0.20	0.024*	0.31	0.730	0.08
	Err	<0.001***	<0.001***	<0.001***	0.130	0.14	0.784	<0.01	0.566	0.14
		Ctrl	**ADHD-R**	**ADHD-P**	**ADHD-P vs Ctrl**		**ADHD-R vs Ctrl**		**ADHD-R vs ADHD-P**	
ALPHA		**p**	**p**	**p**	**p**	**d**	**p**	**d**	**p**	**d**
Average clustering coefficient	*Corr*	0.002**	0.767	0.910	0.086	0.23	0.092	0.36	0.710	0.11
	Err	0.001**	0.599	0.981	0.261	0.16	0.396	0.12	0.696	0.05
Global efficiency	*Corr*	0.728	0.045*	0.004**	0.110	0.23	0.143	0.38	0.716	0.12
	Err	0.155	0.683	0.029*	0.072	0.27	0.193	0.21	0.510	0.08
Path length	*Corr*	0.002**	0.319	0.856	0.127	0.17	0.047*	0.40	0.378	0.24
	Err	0.011*	0.931	0.831	0.075	0.27	0.118	0.29	0.849	<0.01
Mean imaginary coherence	*Corr*	0.020*	0.472	0.491	0.096	0.23	0.111	0.35	0.746	0.11
	Err	0.001**	0.791	0.546	0.061	0.27	0.129	0.25	0.632	0.05

Abbreviations: ADHD-P = ADHD persisters; ADHD-R = ADHD remitters; Corr = trials with correct responses; Ctrl = Control group; d = Cohen's d effect size; Err = trials with incorrect responses; p = random intercept linear model significance testing.
Notes: Random intercept linear models tested for main effects of group (ADHD remitters vs ADHD persisters vs controls), time window (pre-stimulus vs post-stimulus) ad response (correctly- vs incorrectly- responded trials), two-way interactions (group-by-window, group-by-response, time window-by-response), and three-way interactions (group-by-window-by-response) on connectivity measures. Post-hoc tests on within- and between-group effects of change were run only on measures showing a significant group-by-time window interaction. Since this interaction was not significant in diameter in the alpha band and in all measures in the beta band, post-hoc within- and between-groups effects of change were not tested. Age was also included as a covariate of no interest in all analyses. Data in correctly-responded trials were available for 83 ADHD persisters, 22 remitters, 166 controls; and in incorrectly-responded trials for 75 ADHD persisters, 20 remitters, 145 controls.
*$p<0.05$; **$p<0.01$; ***$p<0.001$. $d\geq0.20$ = small effect size, $d\geq0.50$ = medium effect (in italics).*

Table S3.7. Dimensional associations between graph-theory and imaginary coherence measures and interview-based DIVA ADHD symptom counts and clinical impairment within the ADHD group only, controlling for age, gender and IQ

		ADHD symptoms		Impairment	
THETA		**β (95% CIs)**	**p**	**β (95% CIs)**	**p**
Average clustering coefficient	*Pre, Corr*	<0.001 (-0.001;0.001)	0.844	<0.001 (-0.000;0.001)	0.183
	Pre, Err	<0.001 (-0.001;0.001)	0.734	0.001 (-0.000;0.001)	0.065
	Post, Corr	<0.001 (-0.001;0.001)	0.696	<0.001 (-0.000;0.001)	0.290
	Post, Err	-0.001 (-0.002;0.001)	0.343	<0.001 (-0.001;0.001)	0.823
Global efficiency	*Pre, Corr*	<0.001 (-0.001;0.001)	0.637	<0.001 (-0.000;0.001)	0.318
	Pre, Err	<0.001 (-0.001;0.001)	0.856	0.001 (-0.000;0.001)	0.069
	Post, Corr	<0.001 (-0.002;0.001)	0.547	<0.001 (-0.001;0.001)	0.580
	Post, Err	-0.001 (-0.002;0.001)	0.210	-0.001 (-0.001;0.000)	0.159
Path length	*Pre, Corr*	0.040 (-0.123;0.202)	0.632	-0.059 (-0.147;0.028)	0.182
	Pre, Err	-0.031 (-0.168;0.107)	0.664	-0.064 (-0.137;0.008)	0.079
	Post, Corr	0.046 (-0.086;0.178)	0.496	-0.017 (-0.091;0.058)	0.662
	Post, Err	0.041 (-0.059;0.140)	0.425	-0.001 (-0.056;0.055)	0.983
Diameter	*Pre, Corr*	0.082 (-0.181;0.345)	0.540	-0.076 (-0.220;0.070)	0.308
	Pre, Err	-0.062 (-0.288;0.163)	0.589	-0.098 (-0.216;0.020)	0.104
	Post, Corr	0.033 (-0.177;0.244)	0.756	-0.065 (-0.178;0.048)	0.262
	Post, Err	0.060 (-0.112;0.232)	0.495	-0.010 (-0.102;0.081)	0.825
Mean imaginary coherence	*Pre, Corr*	<0.001 (-0.001;0.001)	0.799	<0.001 (-0.000;0.001)	0.207
	Pre, Err	<0.001 (-0.001;0.001)	0.768	0.001 (-0.000;0.001)	0.066
	Post, Corr	<0.001 (-0.002;0.001)	0.642	<0.001 (-0.000;0.001)	0.370
	Post, Err	-0.001 (-0.002;0.001)	0.280	<0.001 (-0.001;0.001)	0.531
		ADHD symptoms		**Impairment**	
ALPHA		**β (95% CIs)**	**p**	**β (95% CIs)**	**p**
Average clustering coefficient	*Pre, Corr*	<0.001 (-0.001;0.001)	0.918	<0.001 (-0.001;0.001)	0.653
	Pre, Err	<0.001 (-0.001;0.001)	0.666	0.001 (-0.001;0.001)	0.151
	Post, Corr	<0.001 (-0.001;0.001)	0.804	<0.001 (0.000;0.001)	0.037*
	Post, Err	0.001 (-0.000;0.001)	0.190	0.001 (0.000;0.001)	0.020*
Global efficiency	*Pre, Corr*	-0.001 (-0.002;0.001)	0.596	<0.001 (-0.001;0.001)	0.587
	Pre, Err	<0.001 (-0.001;0.002)	0.807	0.001 (-0.000;0.002)	0.251
	Post, Corr	<0.001 (-0.001;0.001)	0.852	<0.001 (-0.000;0.001)	0.111
	Post, Err	0.001 (-0.000;0.001)	0.221	0.001 (0.000;0.001)	0.020*
Path length	*Pre, Corr*	-0.004 (-0.212;0.204)	0.969	0.029 (-0.089;0. 481)	0.629
	Pre, Err	-0.011 (-0.153;0.130)	0.876	-0.045 (-0. 121;0.031)	0.246
	Post, Corr	-0.015 (-0.146;0.116)	0.819	-0.060 (-0.129;0.009)	0.090
	Post, Err	-0.061 (-0.115;0.034)	0.208	-0.054 (-0.105;-0.004)	0.036*
Diameter	*Pre, Corr*	-0.051 (-0.365;0.263)	0.749	-0.036 (-0.210;0.138)	0.688
	Pre, Err	-0.083 (-0.302;0.137)	0.461	-0.100 (-0.216;0.017)	0.093
	Post, Corr	-0.035 (-0.253;0.183)	0.751	-0.119 (-0.234;-0.004)	0.043*
	Post, Err	-0.112 (-0.284;0.059)	0.199	-0.092 (-0.184;0.001)	0.053

Mean imaginary coherence	*Pre, Corr*	<0.001 (-0.001;0.001)	0.971	<0.001 (-0.001;0.001)	0.905
	Pre, Err	<0.001 (-0.001;0.002)	0.726	0.001 (-0.000;0.001)	0.175
	Post, Corr	<0.001 (-0.001;0.001)	0.810	<0.001 (0.000;0.001)	0.049*
	Post, Err	0.001 (-0.000;0.001)	0.195	0.001 (0.000;0.001)	0.020*
BETA		**ADHD symptoms**		**Impairment**	
		β (95% CIs)	**p**	**β (95% CIs)**	**p**
Average clustering coefficient	*Pre, Corr*	<0.001 (-0.000;0.001)	0.370	<0.001 (0.000;0.001)	0.029*
	Pre, Err	<0.001 (-0.001;0.001)	0.534	0.001 (0.000;0.001)	0.035*
	Post, Corr	<0.001 (-0.001;0.001)	0.581	<0.001 (-0.000;0.001)	0.096
	Post, Err	<0.001 (-0.001;0.001)	0.592	<0.001 (-0.000;0.001)	0.086
Global efficiency	*Pre, Corr*	<0.001 (-0.001;0.001)	0.433	<0.001 (0.000;0.001)	0.026*
	Pre, Err	<0.001 (-0.000;0.001)	0.572	0.001 (0.000;0.001)	0.031*
	Post, Corr	<0.001 (-0.001;0.001)	0.696	<0.001 (-0.000;0.001)	0.110
	Post, Err	<0.001 (-0.001;0.001)	0.618	<0.001 (-0.001;0.001)	0.087
Path length	*Pre, Corr*	-0.064 (-0.220;0.091)	0.419	-0.081 (-0.165;0.002)	0.057
	Pre, Err	-0.044 (-0.163;0.076)	0.474	-0.064 (-0.127;-0.002)	0.044*
	Post, Corr	-0.036 (-0.188;0.117)	0.649	-0.058 (-0.142;0.025)	0.171
	Post, Err	-0.048 (-0.171;0.075)	0.446	-0.051 (-0.116;0.012)	0.116
Diameter	*Pre, Corr*	-0.136 (-0.387;0.114)	0.286	-0.139 (-0.274;-0.005)	0.042*
	Pre, Err	-0.103 (-0.313;0.106)	0.335	-0.093 (-0.203;0.018)	0.100
	Post, Corr	-0.085 (-0.337;0.168)	0.510	-0.089 (-0.227;0.050)	0.210
	Post, Err	-0.085 (-0.295;0.125)	0.430	-0.067 (-0.177;0.044)	0.238
Mean imaginary coherence	*Pre, Corr*	<0.001 (-0.000;0.001)	0.389	<0.001 (0.000;0.001)	0.028*
	Pre, Err	<0.001 (-0.001;0.001)	0.544	0.001 (0.000;0.001)	0.033*
	Post, Corr	<0.001 (-0.001;0.001)	0.620	<0.001 (-0.000;0.001)	0.102
	Post, Err	<0.001 (-0.001;0.001)	0.604	<0.001 (-0.000;0.001)	0.087

Abbreviations: β = regression coefficient; CIs = confidence intervals; Corr = correctly-responded trials; Err = in correctly-responded trials; p = random intercept linear model significance testing; Pre = pre-stimulus time window; Post = post-stimulus time window.

Notes: Random intercept linear models tested the effect of ADHD symptoms and impairment on each connectivity measure, accounting for sibling relatedness. Data in correctly-responded trials were available for 105 childhood ADHD participants (83 ADHD persisters, 22 remitters); and in incorrectly-responded trials for 95 childhood ADHD participants (75 ADHD persisters, 20 remitters).

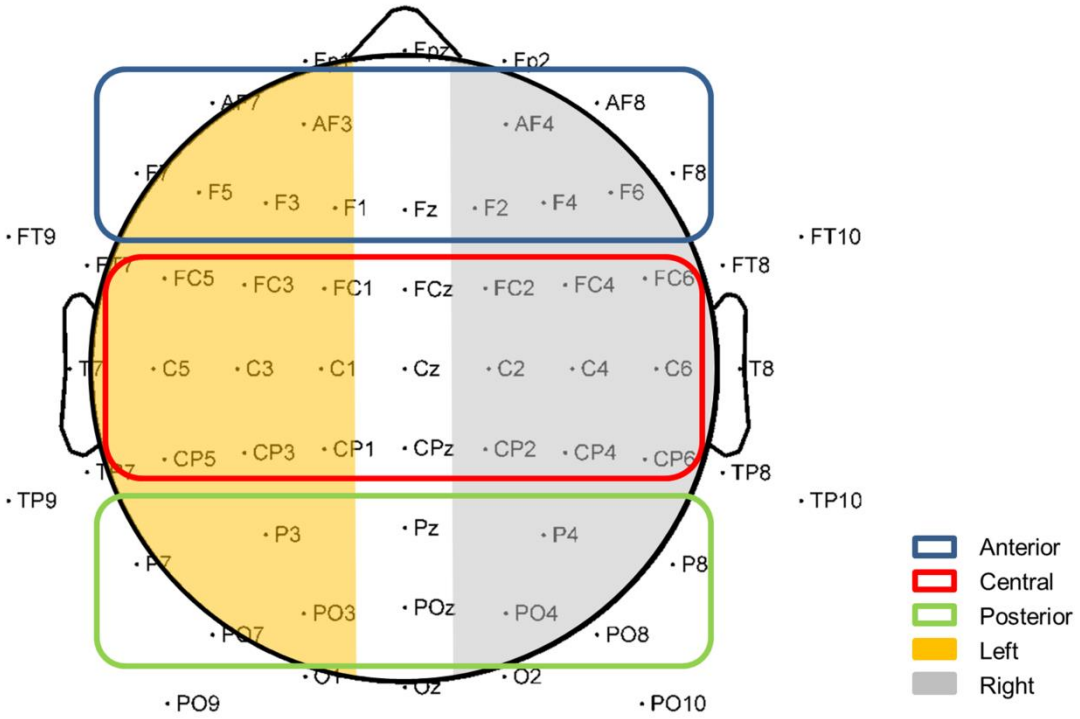

Figure S3.1. *Clusters of electrodes for local connectivity analysis.*

9.8 Appendix B – References

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Appendix C - Chapter 4 supplementary material

10.1 Further information on the sample

Participants for this study are members of the Sibling EEG Follow-Up Study (SEFOS) (Cheung *et al.*, 2016, Michelini *et al.*, 2016), which investigated neurophysiological and cognitive impairments in a follow-up sample of ADHD and control sibling pairs. Adolescents and young adults, who had taken part in the UK subsample of the International Multicenter ADHD Genetics (IMAGE) project (Chen *et al.*, 2008, Cheung *et al.*, 2012, Kuntsi *et al.*, 2010) when they were children, were invited to participate in this follow-up assessment. During the initial study, ADHD participants aged between 6 and 17 years were recruited from specialist clinics in the UK from among those who had a clinical diagnosis of DSM-IV combined subtype ADHD during childhood. Childhood ADHD was assessed based on the Parental Account of Childhood symptoms (PACS) (Taylor *et al.*, 1986a, Taylor *et al.*, 1986b), a semi-structured, standardised, investigator interview with high inter-rater reliability, to establish the research diagnosis of DSM-IV combined-type ADHD in childhood. Closest-age siblings were also then recruited and assessed for ADHD using the same procedures. A control group, which was initially recruited from primary (ages 6-11 years) and secondary (ages 12-18 years) schools in the UK (Kuntsi *et al.*, 2010), was also invited to take part in this follow up study. The total sample in childhood consisted of 267 participants from ADHD sibling pairs and 258 participants from control sibling pairs (n=525 participants). Exclusion criteria included IQ<70, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. All participants were of European Caucasian decent. At follow up, participants were contacted by telephone and scheduled for a single testing session including clinical, cognitive and EEG assessments. Retention rate at follow-up was 77%.

10.2 ERP analysis

ERP measures which showed ADHD-control differences in our previous work on this sample were included in this study (Cheung *et al.*, 2017, Cheung *et al.*, 2016, Michelini *et al.*, 2016). ERPs from the cued performance task (CPT-OX) included the Cue-P3, the CNV and the NoGo-P3 (Cheung *et al.*, 2016). The Cue-P3 amplitude was measured as the maximum positive peak

between 250-600ms following cue trials at Pz. The CNV was analysed as mean amplitudes between 1300 and 1650ms following cues at Cz. The NoGo-P3 amplitude was measured as the maximum positive peak between 250-600 ms following NoGo trials at Cz. As in our previous work (Michelini *et al.*, 2016), ERPs from the arrow flanker task included the N2, the ERN and the Pe from the incongruent condition only, as an N2 reduction in ADHD compared to neurotypical individuals is only observed in the incongruent condition (but not in the congruent condition) of this task (Albrecht *et al.* 2008; McLoughlin *et al.* 2009), and a sufficient number of errors to allow at least 20 ERP segments for robust ERP averaging is made in incongruent trials only (McLoughlin *et al.* 2009). The N2 amplitude was measured as maximum negative peak at Fz and FCz between 250-450 ms after target onset. The ERN amplitude was defined with respect to the preceding positivity (PNe, -100-50 ms) (Albrecht *et al.*, 2008, McLoughlin *et al.*, 2009, Nieuwenhuis *et al.*, 2001), and was measured at FCz between 0-150 ms. The Pe amplitude was measured as maximum positive peak at CPz between 150-450 ms. The baseline-P3 was extracted from the baseline condition of the Fast task, and measured as the area amplitude measure at Pz between 250 and 450 ms (Cheung *et al.*, 2017). CNV, Cue-P3, NoGo-P3, N2 and baseline-P3 were stimulus-locked and measured on correct trials only, while the ERN and Pe were response-locked and measured when an erroneous response was made.

10.3 Further information on the exploratory factor analysis (EFA)

Our analysis started with an examination of the correlated factors solution of the Cholesky decomposition, which gives separate correlation matrices for the underlying familial and non-familial influences. On the basis of the familial and non-familial correlation matrices between all 9 cognitive-ERP measures, data were simulated in R for 1000 participants within two EFAs, separately for familial and non-familial influences. EFA approaches give an indication of the underlying factor structure, but no specification of the underlying covariance matrices can be deduced. Factors were extracted using an unweighted least squares estimator approach following previous work (Loken *et al.*, 2014). An unweighted least squares estimator was chosen over other extraction methods as it has shown robust as a method of factor analysing ordinal data yielding polychoric correlations (Forero *et al.*, 2009, Lee *et al.*, 2012). Factors with an eigenvalue of greater than 1 (Figure S4.1) were extracted and rotated using an oblique (oblimin) rotation, which allows correlation between factors. The extracted factor structure and factor loadings (Table S4.3) were specified separately for familial and non-familial influences in a

confirmatory factor model in OpenMx. This confirmatory model was aimed at examining the covariation between the factors capturing the cognitive-ERP measures and ADHD.

10.4 Further explanation on constrained correlation bivariate models and variable selection

Using our large cognitive battery, previous phenotypic analyses on this sample found that individuals with ADHD showed atypical profiles, compared to controls, in the following 22 cognitive and ERP variables (Cheung *et al.*, 2017, Cheung *et al.*, 2016, Michelini *et al.*, 2016): commission errors, omission errors, mean reaction time (MRT), reaction time variability (RTV), Cue-P3, NoGo-P3 and CNV from the CPT-OX; number of errors in congruent trials (congruent error) and in incongruent trials (incongruent errors), MRT and RTV in both congruent and incongruent conditions, N2, ERN and Pe from the incongruent condition of the arrow flanker task; MRT, RTV and P3 from the baseline condition of the Fast task; IQ and digit span forward and backward. In multivariate analyses, due to constraints in the number of variables that can be included in a multivariate SEM model, it was not possible to include all measures (similar to previous quantitative genetic analyses on neurocognitive data; Frazier-Wood *et al.*, 2012, Kuntsi *et al.*, 2010, McLoughlin *et al.*, 2014). Since our aim was to identify measures associated with ADHD and that would inform on the underlying familial relationships with the disorder, preliminary analyses were thus carried out to objectively select variables more strongly related to ADHD and that showed evidence of underlying familial influences. We ran constrained correlation bivariate models between ADHD and each of the 22 cognitive-ERP variables (Table S4.1) extracted from our large cognitive-neurophysiological battery, in order to select variables that had (1) modest-to-large (Cohen, 1988) phenotypic correlation with ADHD (phenotypic correlation above .20) and (2) significant cross-sibling/within-trait sibling correlations, suggesting the influence of familial factors (Table S4.1). These models give maximum likelihood estimates of correlations between two traits within and across pairs while applying specific constraints. Applied constraints reflect the assumptions of the familial model, i.e. that phenotypic correlations across traits within individuals are the same across siblings and that cross-sibling/cross-trait correlations are independent of sibling order. Given the selected nature of this sample (selection of ADHD probands) and ADHD modelled as present/absent, we further included constraints reflecting the assumptions of the liability distributions underlying ADHD status: we fixed the sibling correlation for ADHD status to .40 and the threshold on ADHD liability

to a z-value of 1.64, corresponding to a population prevalence of 5%. Cognitive-ERP variables were modelled as continuous if their age- and sex- residuals were normally distributed or could be normalised using transformations methods, and included with ADHD status in combined continuous-ordinal bivariate models. In these analyses, a model for the thresholds of ordinal variables in specified along with a model for the means of continuous variables. Cognitive-ERP variables which could not be normalised using any transformation methods were modelled as ordinal using equal-sized categories, and included with ADHD status in bivariate ordinal liability-threshold models, estimating age and sex effects on their mean. Ordinal models and combined continuous-ordinal models were used to derive, respectively, the polychoric and polyserial phenotypic correlations between ADHD and each cognitive-ERP variable, the cross-sibling/within-trait sibling correlation for each cognitive-ERP variable, and the cross-sibling cross-trait sibling correlation between ADHD and each cognitive-ERP variable (Table S4.1).

Information about the precision of parameter estimates was obtained by likelihood-based confidence intervals (CIs). According to the criteria outlined above, IQ, DSF, DSB; MRT and RTV from the Fast task (baseline condition); RTV, OE and NoGo-P3 (Figure S4.3) from the CPT-OX; and RTV in the congruent and incongruent condition, congruent errors (CongE) and ERN (Figure S4.2) from the arrow flanker task could be retained for inclusion with ADHD status in the multivariate models, as they met both inclusion criteria. Since all measures of RTV across tasks showed large correlations with one another (r=.45-.76), only RTV from the baseline condition of the Fast task was included, as this variable showed the strongest phenotypic correlation with ADHD (Table S4.1).

10.5 Model comparisons

The Akaike information criterion (AIC) and χ^2 difference tests were used to inform on model fit when comparing models. The confirmatory 3-factor model showed a significantly better fit compared to the Cholesky decomposition (p=.08) (Table S4.4), indicating support for this more parsimonious description of the data. As a sensitivity test, the 3-factor model was also compared to a 1-factor model. In this 1-factor model, all cognitive-ERP variables were influenced by 1 familial factor and 1 non-familial factor, with correlation paths to the familial and non-familial influences on ADHD, respectively. The 1-factor model provided a significantly worse fit than the 3-factor model (p<.01). This suggests that, although the 3 familial and non-familial factors are

inter-correlated, they represent processes that are at least partly separable and cannot be accounted for by a single factor.

10.6 Proportion of phenotypic correlation due to familial and non-familial factors

The proportion of phenotypic correlation between ADHD and each cognitive-ERP variable explained by contributions of shared familial and non-familial influences could be further derived from the factor model (note that these phenotypic correlations could be slightly different from those estimated from the saturated Cholesky model in Table 4.1 in Chapter 4). For example, the proportion of phenotypic correlation between IQ and ADHD is calculated by two pathways: (1) via linked familial factors: the product of the standardised factor loading of IQ (path from cF1 to IQ), the correlation between cF1 and the ADHD-specific familial factor, and the standardized factor loading of ADHD (√.40), [-.64*.50*√.40=-.20]; and (2) via linked non-familial factors: [.43*-.40*√.60=-.13]. These two pathways sum up to the predicted phenotypic correlation according to this model, and the proportions of familial and non-familial overlap work out to be -.20/-.34=60% and -.13/-.34=40%, respectively. Note that proportions can only be derived if the contributions have the same sign. All correlations were similarly explained by shared familial and non-familial factor influences (Table S4.5).

Table S4.1. Constrained correlation sibling models of all cognitive-neurophysiological measures

	r_{Ph} with ADHD	Sibling r	Cross-sib/cross-trait r with ADHD
CPT-OX			
OE	**0.30 (0.18; 0.42)**	**0.22 (0.03;0.40)**	**0.26 (0.13; 0.39)**
CE	**0.14 (0.01; 0.26)**	0.11 (-0.09; 0.30)	0.11 (-0.03; 0.23)
MRT	**0.19 (0.09; 0.30)**	**0.25 (0.10; 0.39)**	0.09 (-0.03; 0.20)
RTV	**0.28 (0.16; 0.38)**	**0.27 (0.13; 0.40)**	**0.16 (0.05; 0.27)**
Cue-P3	-0.16 (-0.27; -0.05)	0.14 (-0.02; 0.28)	0.03 (-0.08; 0.15)
CNV	**0.25 (0.13; 0.34)**	0.14 (-0.03; 0.31)	0.08 (-0.04; 0.20)
NoGo-P3	**-0.25 (-0.36; -0.14)**	**0.25 (0.10; 0.39)**	**-0.16 (-0.31; -0.04)**
Fast task			
MRT-baseline	**0.35 (0.24; 0.45)**	**0.32 (0.18; 0.44)**	**0.15 (0.03; 0.26)**
RTV-baseline	**0.44 (0.34; 0.54)**	**0.28 (0.13; 0.41)**	**0.19 (0.07; 0.30)**
P3-baseline	-0.07 (-0.19; 0.06)	**0.26 (0.09; 0.42)**	-0.03 (-0.16; 0.10)
Flanker task			
CongE	**0.33 (0.20; 0.43)**	**0.22 (0.04; 0.38)**	**0.13 (0.00; 0.25)**
IncongE	**0.22 (0.10; 0.33)**	0.10 (-0.05; 0.25)	**0.14 (0.02; 0.25)**
MRT-cong	**0.17 (0.05; 0.28)**	**0.22 (0.06; 0.36)**	0.05 (-0.07; 0.17)
MRT-incong	**0.13 (0.01; 0.24)**	**0.24 (0.09; 0.37)**	0.03 (-0.09; 0.16)
RTV-cong	**0.35 (0.24; 0.45)**	**0.21 (0.07; 0.34)**	**0.12 (0.01; 0.23)**
RTV-incong	**0.35 (0.24; 0.45)**	**0.20 (0.05; 0.33)**	**0.14 (0.03; 0.25)**
N2	**0.14 (0.03; 0.26)**	**0.29 (0.14; 0.43)**	0.07 (-0.04; 0.20)
ERN	**-0.24 (-0.35; -0.12)**	**0.21 (0.04; 0.36)**	-0.09 (-0.21; 0.03)
Pe	**-0.19 (-0.30; -0.06)**	**0.24 (0.08; 0.40)**	-0.06 (-0.19; 0.07)
IQ and Digit Span			
IQ	**-0.38 (-0.48; -0.27)**	**0.50 (0.39; 0.60)**	**-0.17 (-0.28; -0.06)**
DSF	**-0.23 (-0.35; -0.11)**	**0.45 (0.32; 0.56)**	**-0.14 (-0.25; -0.01)**
DSB	**-0.30 (-0.41; -0.19)**	**0.30 (0.15; 0.43)**	**-0.22 (-0.33; -0.10)**

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CE, commission errors from the cued continuous performance test; CongE, errors in the congruent condition of the flanker task; CPT-OX, cued continuous performance test; Cross-sib/cross-trait r with ADHD, cross-

sibling/cross-trait correlation between each variable and ADHD; Cue-P3, P3 amplitude in the Cue condition of the cued continuous performance test; DSB, digit span backward; DSF, digit span forward; ERN, error-related negativity amplitude from the flanker task; IQ, intelligence quotient; IncongE, errors in the incongruent condition of the flanker task; MRT, mean reaction time from the cued continuous performance test; MRT-baseline, mean reaction time from the baseline condition of the Fast task; MRT-cong, mean reaction time from the congruent condition of the flanker task; MRT-incong, mean reaction time from the incongruent condition of the flanker task; N2, N2 component amplitude from the flanker task; NoGo-P3, P3 amplitude in the NoGo condition from the cued continuous performance test; OE, omission errors from the cued continuous performance test; P3-baseline, P3 amplitude from the baseline condition on the Fast task; Pe, error positivity amplitude from the flanker task; r_{Ph} with ADHD, phenotypic correlation with ADHD; RTV, reaction time variability from the cued continuous performance test; RTV-baseline, reaction time variability from the baseline condition of the Fast task; RTV-cong, reaction time variability from the congruent condition of the flanker task; RTV-incong, reaction time variability from the incongruent condition of the flanker task; Sibling r, correlation between siblings on each variable.

Notes: significant ($p<0.05$) values are given in bold. Variables included in the multivariate factor analysis are highlighted in grey.

Table S4.2. Descriptive statistics for cognitive-neurophysiological measures divided by group, with test for statistical difference

	ADHD probands (n=87)	Unaffected siblings (n=100)	Controls (n=169)	p	ADHD probands vs Controls	ADHD probands vs Unaffected siblings	Unaffected siblings vs Controls
					p	p	p
IQ	96.30 (15.23)	102.85 (14.19)	109.79 (12.45)	**<.001**	**<.001**	**<.01**	**<.001**
MRT	626.35 (142.81)	576.46 (125.81)	546.48 (118.90)	**<.001**	**<.001**	**<.001**	**.009**
RTV	183.16 (129.66)	127.76 (86.52)	102.75 (82.60)	**<.001**	**<.001**	**<.001**	**<.001**
OE	2.86 (4.15)	1.19 (1.88)	0.75 (1.53)	**<.001**	**<.001**	**.02**	**<.001**
CongE	9.54 (13.12)	5.14 (5.77)	4.24 (8.27)	**<.001**	**<.001**	**.001**	**.02**
DSF	9.27 (2.09)	9.82 (2.14)	10.41 (2.11)	**<.001**	**<.001**	.10	**.01**
DSB	6.26 (2.42)	6.79 (2.22)	7.96 (2.62)	**<.001**	**<.001**	.06	**<.001**
ERN	7.96 (3.67)	9.76 (4.42)	10.36 (4.73)	**<.001**	**<.001**	**.008**	.24
NoGo-P3	6.82 (4.50)	7.92 (3.52)	8.93 (3.69)	**<.001**	**<.001**	**.004**	.26

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CongE, number of errors in the congruent condition of the flanker task; DSB, digit span backward; DSF, digit span forward; ERN, error-related negativity amplitude from the flanker task; IQ, intelligence quotient; MRT, mean reaction time from the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued continuous performance test; OE, number of omission errors from the cued continuous performance test; RTV, reaction time variability from the Fast task.

Notes: Significant (p<0.05) differences are indicated in bold. Group differences between ADHD and control participants on this sample were reported in previous analyses (Cheung et al., 2016, Michelini et al., 2016).

Table S4.3. Loadings of extracted familial and non-familial factors from the EFAs

	Familial factors			**Non-familial factors**		
	F1	F2	F3	F1	F2	F3
% Var	53.19	16.27	12.10	32.01	15.72	11.91
	Factor loadings			**Factor loadings**		
IQ	**-0.52**	0.33	0.07	-0.09	**0.61**	0.13
DSF	0.03	**0.99**	0.04	.06	**0.55**	-0.09
DSB	-0.38	**0.67**	0.03	.02	**0.44**	-0.08
ERN	-0.16	-0.24	**0.85**	.07	0.03	**-0.64**
NGP3	0.07	0.17	**0.38**	-.06	-0.01	**-0.48**
MRT	**0.92**	-0.01	-0.05	**0.96**	-0.04	-0.03
RTV	**0.98**	0.06	-0.06	**0.82**	0.01	0.15
OE	0.14	-0.17	**-0.66**	0.12	0.06	**0.50**
CongE	0.02	0.06	**-0.80**	0.05	-0.22	**0.42**
	Factor correlations			**Factor correlations**		
F1	1			1		
F2	-0.31	1		-0.22	1	
F3	-0.52	0.32	1	0.45	-0.38	1

Abbreviations: % Var, percentage of variance explained by each factor; ADHD, attention-deficit/hyperactivity disorder; CongE, errors in the congruent condition of the flanker task; DSB, digit span backward; DSF, digit span forward; ERN, error-related negativity amplitude from the flanker task; F1, factor 1; F2, factor 2; F3, factor 3; IQ, intelligence quotient; MRT, mean reaction time from the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued continuous performance test; OE, omission errors from the cued continuous performance test; RTV, reaction time variability from the Fast task.

Note: the largest factor loadings for each variable are given in bold.

Table S4.4. Model comparisons

Model	EP	-2LL	df	AIC	BIC	m.o.c.	χ^2	df	p
1. Cholesky	126	8163.76	3438	1287.75	-10284.47	-	-	-	-
2. 3-Factor	**64**	**8242.29**	**3500**	**1242.29**	**-10538.63**	**1**	**78.53**	**62**	**.08**
3. 1-Factor	55	8320.92	3509	1302.92	-10508.29	2	78.63	9	<.01

Abbreviations:AIC, Akaike information criterion; BIC, Bayesian information criterion; EP, number of estimated parameters; -2LL, -2 log likelihood statistic; df, degrees of freedom; m.o.c., model of comparison; χ^2, difference in log likelihood statistic.
Note: the best fitting model is inidicated in bold.

Table S4.5. Proportion of phenotypic correlation between cognitive-ERP variables and ADHD explained by familial and non-familial influences, with 95% confidence intervals in brackets

	Phenotypic correlation with ADHD	Explained by shared familial effects	Explained by shared non-familial effects
IQ	-0.33 (-0.44; -0.23)	0.60 (0.35;0.82)	0.40 (0.18;0.65)
DSF	-0.25 (-0.35; -0.15)	0.49 (0.15;0.75)	0.51 (0.25;0.86)
DSB	-0.27 (-0.37; -0.17)	0.49 (0.13;0.75)	0.51 (0.25;0.87)
ERN	-0.26 (-0.33; -0.17)	0.49 (0.22;0.75)	0.51 (0.24;0.78)
NoGo-P3	-0.22 (-0.30; -0.13)	0.41 (0.08;0.76)	0.59 (0.24;0.78)
MRT	0.37 (0.27; 0.46)	0.40 (0.20;0.62)	0.60 (0.38;0.80)
RTV	0.37 (0.26; 0.46)	0.41 (0.20;0.63)	0.59 (0.37;0.80)
OE	0.35 (0.23; 0.44)	0.65 (0.38;0.86)	0.35 (0.15;0.62)
CongE	0.30 (0.19; 0.39)	0.42 (0.13;0.75)	0.58 (0.25,0.87)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CongE, errors in the congruent condition of the flanker task; DSB, digit span backward; DSF, digit span forward; ERN, error-related negativity amplitude from the flanker task; IQ, intelligence quotient; MRT, mean reaction time from the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued continuous performance test; OE, omission errors from the cued continuous performance test; RTV, reaction time variability from the Fast task.
Note: All values are significant ($p<0.05$).

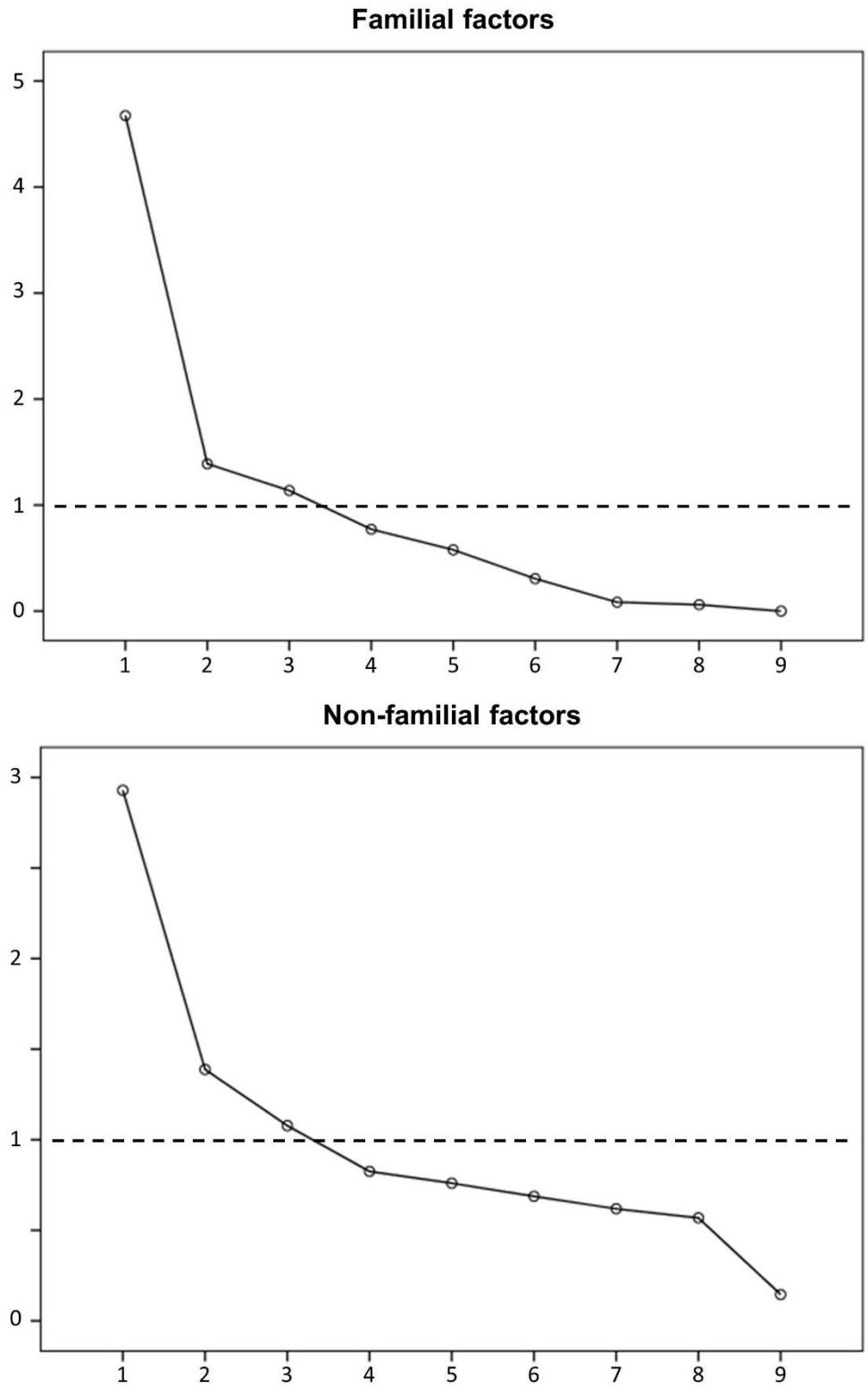

Figure S4.1. *Scree plots of Exploratory Factor Analysis for familial (top half) and non-familial (bottom half) factors.*

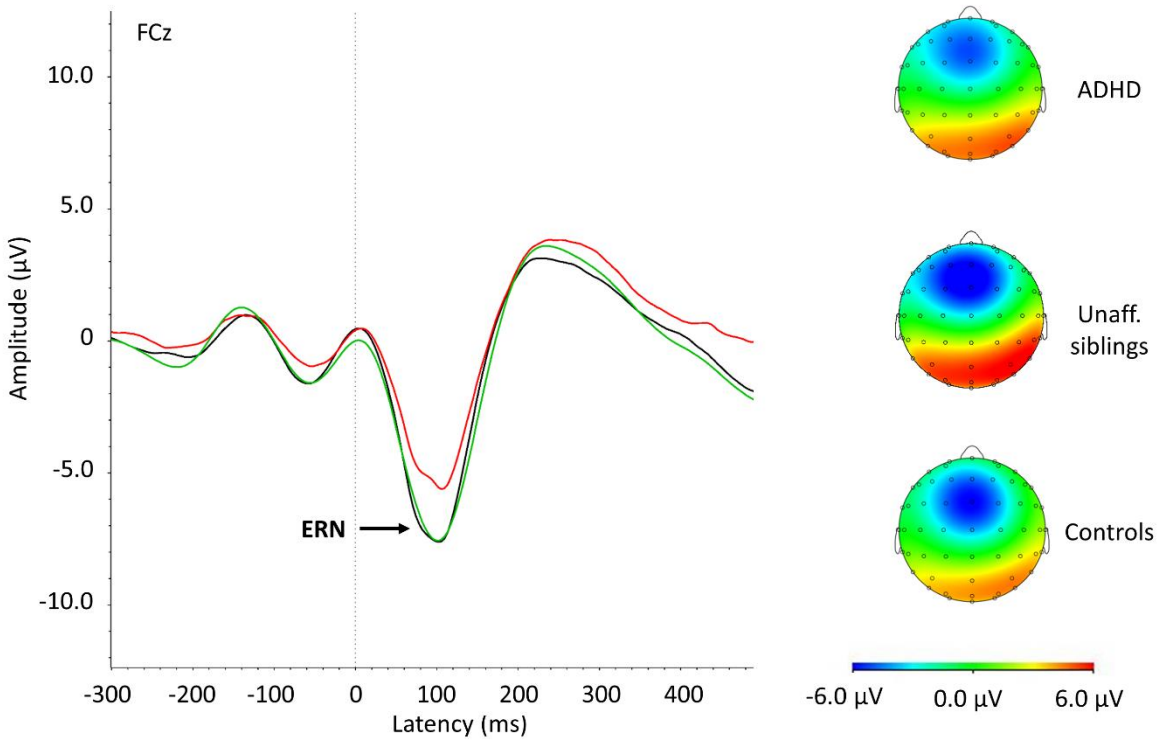

Figure S4.2. *Grand average response-locked ERPs of the ERN at FCz electrode between 0-150 ms after an erroneous response on the incongruent trials for individuals with ADHD (in red), unaffected siblings of ADHD probands (in green) and control participants (in black), with topographic maps.*

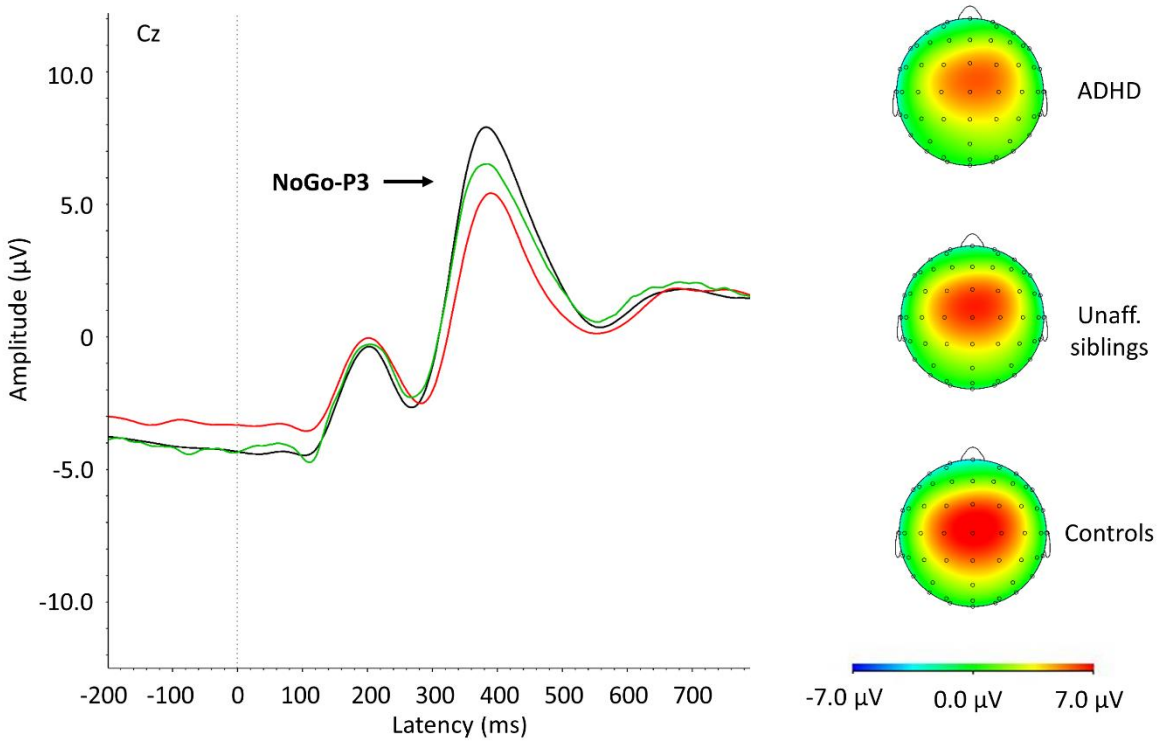

Figure S4.3. *Grand average stimulus-locked ERPs of the NoGo-P3 at Cz electrode between 250-600 ms for individuals with ADHD (in red), unaffected siblings of ADHD probands (in green) and control participants (in black), with topographic maps.*

10.7 Appendix C – References

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Appendix D - Chapter 5 supplementary material

11.1 Number of artefact-free segments included in each condition

The average number of segments in each group for the Cue, NoGo and Go conditions is reported in Table S5.1. The number of segments was entered into univariate ANOVA to check for group differences, with "group" as between-subjects variable (ADHD, BD and control participants). Groups did not differ on the number of artefact-free segments for the Cue condition [F(2, 57)=0.30, p=0.75], the NoGo condition [F(2, 57)=0.15, p=0.87] or Go condition [F(2, 55)=0.49, p=0.62].

11.2 Analysis of ERP parameters without baseline correction

The majority of previous ERP analyses on CPT-OX in ADHD samples did not apply a baseline subtraction (Banaschewski *et al.* 2004; McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013). In this study, we chose to apply a baseline correction in order to reduce the influence of pre-stimulus activity on our ERP measures. However, analyses were also repeated without baseline correction in order to allow comparison with previous results.

Cue condition

A trend-level effect of group emerged for the Cue-P3 [F(2,57)=2.48, p=0.09]. Post-hoc comparisons showed a significant difference between the ADHD and the BD group (p=0.03), with large effect size (Table S5.2). The control group did not differ from either the ADHD (p=0.59) or the BD (0.14) groups.

A significant effect of group emerged for the CNV [F(2,57)=3.68, p=0.03]. Post-hoc comparisons showed a significant difference between the ADHD and the control group (p=0.01), with large effect size (Table S5.2). The BD group did not differ from either the ADHD (p=0.22) or the control (0.15) groups.

NoGo condition

A significant effect of group on the NoGo-N2 [F(2,57)=5.12, p=0.01]. Post-hoc analyses revealed that BD participants significantly differed from ADHD (p=0.01) and control (p=0.02) participants, both with large effect sizes (Table S5.2). The ADHD and the control groups did not differ from each other (p=0.68).

A significant effect of group emerged on the NoGo-P3 [F(2,57)=3.35, p=0.04]. Post-hoc analyses showed that both ADHD (p=0.05) and BD (p=0.02) participants significantly differed from controls, respectively with medium and large effect sizes (Table S5.2), but not from each other (p=0.55).

Go condition

No significant effect of group emerged on the Go-P3 [F(2,55)=0.61, p=0.55].

11.3 Comparison with results of data with baseline correction

Results of data without baseline correction (Table S5.2) showed a reduced Cue-P3 in participants with BD compared to participants with ADHD, which was not observed in data with baseline correction. No difference emerged between the BD and control groups in the CNV, which was at trend level in results of data with baseline correction. Group differences in ERPs from the NoGo and Go conditions remained the same.

Of note, an ADHD-control difference in the Cue-P3 was not found when analysing data with or without baseline correction. Although this difference has been reported in previous studies using this task when a baseline subtraction was not applied (Banaschewski *et al.* 2004; McLoughlin *et al.* 2010, 2011; Albrecht *et al.* 2013; Doehnert *et al.* 2013), this discrepancy is likely not due to the use of baseline correction. Possible explanations for the lack of ADHD-control difference in the Cue-P3 in this sample are discussed in the main text (see Discussion section).

Table S5.1. Mean (SD) number of artefact-free segments in each ERP average by group and condition during the CPT-OX

	ADHD (n=20)* mean (SD)	**BD (n=20)** mean (SD)	**Controls (n=20)** mean (SD)
Cue	58.35 (11.65)	60.10 (10.28)	60.80 (9.05)
NoGo	30.75 (3.78)	30.05 (4.73)	30.30 (3.85)
Go	29.22 (5.99)	29.20 (5.29)	30.65 (4.87)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder.
**Only 18 ADHD participants were included in the average of the Go condition, as two subjects did not have at least 20 artefact-free segments.*

Table S5.2. ERP measures from the CPT-OX (without baseline correction): means (SDs), effect sizes (Cohen's d) and significance of group comparisons

	ADHD (n=20)* mean (SD)	**BD (n=20)** mean (SD)	**Controls (n=20)** mean (SD)	**ADHD vs. BD** effect size (d)	**ADHD vs. Controls** effect size (d)	**BD vs. Controls** effect size (d)
Cue-P3 at Pz	1.73 (1.37)	0.72 (1.41)	1.47 (1.67)	**0.75***	0.18	*0.50*
CNV at Cz	-2.33 (1.02)	-2.79 (1.29)	-3.50 (1.74)	0.41	**0.85***	*0.48*
NoGo-N2 at Fz	-0.45 (0.96)	0.90 (1.94)	-0.64 (1.88)	**0.90***	0.13	**0.83***
NoGo-P3 at Cz	3.33 (1.92)	2.93 (2.34)	4.50 (1.69)	0.19	*0.67**	**0.79***
Go-P3 at CPz	2.77 (2.76)	3.20 (2.85)	3.63 (2.11)	0.17	0.41	0.18

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CNV, contingent negative variation.
*Notes: mean and SD were calculated on raw data. Large effect sizes are given in bold, medium effect sizes are given in italics; *p<0.05, †p<0.10; results changing compared to analysis of data with baseline correction are underlined.*
**Only 18 participants with ADHD were included in the average of the Go condition, as two participants did not have at least 20 artefact-free segments.*

11.4 Appendix D – References

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Appendix E - Chapter 6 supplementary material

12.1 Analysis of length-matched cognitive-performance indices

The two conditions were not matched on task length, but were matched on the number of trials. The fore-period in the baseline condition (8 s) was longer than in the fast-incentive condition (1 s). This difference was specifically designed to probe sustained attention and vigilance in attention-deficit/hyperactivity disorder (ADHD) samples in the baseline condition, and test improvements with shorter fore-periods. To exclude the possibility that differences between conditions may be due to differential task length, we analysed reaction time variability (RTV) performance on both the full baseline condition (presented in the main text) and separately on the length-matched segment, consistent with our previous studies on this task (Andreou et al., 2007, Cheung et al., 2017, Kuntsi et al., 2013). Data from 30 trials of the baseline condition were used, to provide a match on length of time on task with the fast-incentive condition. The second set of 30 trials are used for this analysis, as this segment of the baseline condition was considered more reliable than the first set of 30 trials, which is likely a reflection of an initial learning phase during the first part of the task (Andreou et al., 2007). Since the fast-incentive condition was always administered after the baseline condition, it did not involve a similar learning phase.

A significant main effect of group ($p=0.004$) and condition ($p<0.001$), but no group-by-condition interaction ($p=0.69$) emerged, with both the ADHD and the bipolar disorder (BD) groups showing increased RTV compared to the control group, but no differences between clinical groups, in the length-matched baseline condition (ADHD vs BD: d=0.44, 95% CIs=-0.19–1.07, p=0.17; ADHD vs Control: d=1.04, 95%, CIs=0.35–1.71, p=0.003; BD vs Control: d=0.61, 95% CIs=-0.04–1.26, p=0.067). All three groups showed significant within-group differences between conditions (all $p<0.003$), but no group differences in the degree of change between conditions (ADHD vs BD: d=0.22, 95% CIs=-0.41–0.84, p=0.50; ADHD vs Control: d=0.29, 95% CIs=-0.35–0.62, p=0.37; BD vs Control: d=0.17, 95% CIs=-0.47–0.81, p=0.595).

These additional analyses show that comparable results to those in the full baseline were obtained for RTV using the length-matched segment of the baseline condition (Andreou et al., 2007, Cheung et al., 2017).

12.2 Further details on the analysis of event-related spectral perturbation (ERSP) indices

In time-frequency analyses, the modulations of EEG frequency components in response to a stimulus are normalised with respect to spectral power in a pre-defined pre-stimulus period. Specifically, the post-stimulus power at each time-frequency point is divided by the mean spectral power in the pre-stimulus period (typically reflecting spontaneous EEG) at the same frequency (Herrmann et al., 2014, Grandchamp and Delorme, 2011). The normalised post-stimulus signal is scaled in decibel (dB), a logarithmic unit that represents the ratio of two signals. When comparing the ERSPs in two conditions, it is necessary to match the pre-stimulus period used to normalise the post-stimulus ERSPs (Herrmann et al., 2014). In the present study, to compare the ERSPs in the baseline and fast-incentive conditions, we matched the timing of the pre-stimulus window across the two conditions (-2 to -1 s) with respect to the appearance of the target stimulus (Figure S6.1). This window represents the -1 to 0 s period before the warning stimulus appearing 1 s before the target in the fast-incentive condition, reflecting a window of spontaneous EEG activity before warning and target onsets. The same corresponding -2 to -1 s window in the baseline condition similarly represents a period of spontaneous EEG activity during the long fore-period between the appearance of the warning and of the target. This window in the baseline condition was chosen instead of the corresponding pre-warning window in the baseline condition (-9 to -8 ms) because segmenting the data around the target from the pre-warning window in the baseline condition to the post-target period (-9 to 1 s after the target) would have produced too few of such long segments for analyses in the baseline condition.

12.3 Analysis of pre-stimulus theta inter-trial phase coherence (ITC) in the fast-incentive condition

Since a difference between groups emerged in target-related theta ITC in the fast-incentive condition, we carried out an additional analysis to examine whether these differences could be attributed to differences in the phase of theta prior to target onset. Theta ITC data were calculated as described in the main text, and examined in the -500-0 ms window before appearance of target stimuli. We investigated pre-target theta ITC and post-target theta ITC (measured as described in the main text) in a random intercept linear model, testing for main

effects of group (ADHD vs BD vs control), time window (pre-target vs post-target) and group-by-window interactions.

A significant effect of time window ($p<0.001$) and group-by-window interaction ($p<0.001$), but not main effect of group ($p=0.38$), emerged for theta ITC. Post-hoc tests showed that groups did not differ in the pre-target time window (overall group effect: $p=0.17$), but the control group had significantly greater ITC than the ADHD and BD groups in the post-target time window, as reported in the main text. All three groups showed a significant increase in theta ITC from the pre-target to the post-target time window (all $p<0.001$), but the control group showed a greater degree of change between time windows than the ADHD ($d=1.05$, $p=0.003$) and BD ($d=1.10$, $p=0.002$) groups. The ADHD and BD groups did not differ in the change between time windows ($d=0.08$, $p=0.81$).

These further analyses indicate that greater phase consistency following target stimuli in the control group, compared to the clinical groups, cannot be attributed to differences in the pre-target window; in the pre-target window, all groups show lower theta ITC values than in the post-target window, as expected (Mazaheri and Picton, 2005, Makeig et al., 2004b), but no group differences. Greater phase consistency upon target presentation in the control group, relative to the clinical groups, may therefore suggest that controls consistently showed a reset and alignment in phase of theta oscillations (as indicated by the within-group increase in phase consistency from pre-target to post-target windows) over trials. This mechanism of phase-resetting has been previously associated with optimal behavioural performance (Biau et al., 2015, Palaniyappan et al., 2012, Lakatos et al., 2009). This process may be less consistent across trials in both disorders, as suggested by a lower degree of change from pre-target to post-target and lower phase consistency in theta oscillations in ADHD and BD groups than controls. These differences point to suboptimal regulation of this neural process in women with ADHD and women with BD.

Table S6.1. Descriptive statistics on study variables divided by group

	Baseline condition						Fast-incentive condition					
	ADHD		BD		Ctrl		ADHD		BD		Ctrl	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RTV	374.44	288.19	289.28	175.80	232.35	240.20	176.87	145.83	132.75	68.83	114.78	79.13
CNV	-0.35	0.51	-0.35	0.63	-0.33	0.54	-0.79	0.64	-1.29	0.98	-1.84	0.91
P3	531.58	459.56	501.53	359.17	531.72	496.91	465.10	307.51	427.19	310.80	618.51	388.27
Theta ERSP (0-500 ms, CP)	1.22	0.69	1.41	0.83	1.54	0.92	0.74	0.76	1.02	0.80	1.31	0.98
Alpha ERSP (0-500 ms)	-0.77	1.05	-0.93	1.26	-1.12	1.58	-0.64	0.82	-0.63	0.81	-0.83	1.42
Alpha ERSP (500-1000 ms)	-1.69	1.38	-1.99	1.78	-2.13	1.99	-0.74	0.95	-0.77	1.34	-1.73	1.86
Beta ERSP (0-500 ms)	-0.98	0.55	-0.76	0.59	-1.03	0.69	-1.13	0.68	-0.77	0.45	-1.23	0.70
Beta ERSP (500-1000 ms)	-1.27	0.71	-0.94	1.41	-0.94	0.92	-0.59	0.71	-0.52	1.13	-0.58	1.02
Theta ITC (0-500 ms)	0.25	0.06	0.26	0.05	0.28	0.06	0.28	0.07	0.29	0.06	0.33	0.06

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CNV, contingent negative variation; CP, centro-parietal region; Ctrl, control group; ERSP, event-related spectral perturbation; ITC, inter-trial phase coherence; MRT, mean reaction time; RTV, reaction time variability.SD, standard deviation of the mean.

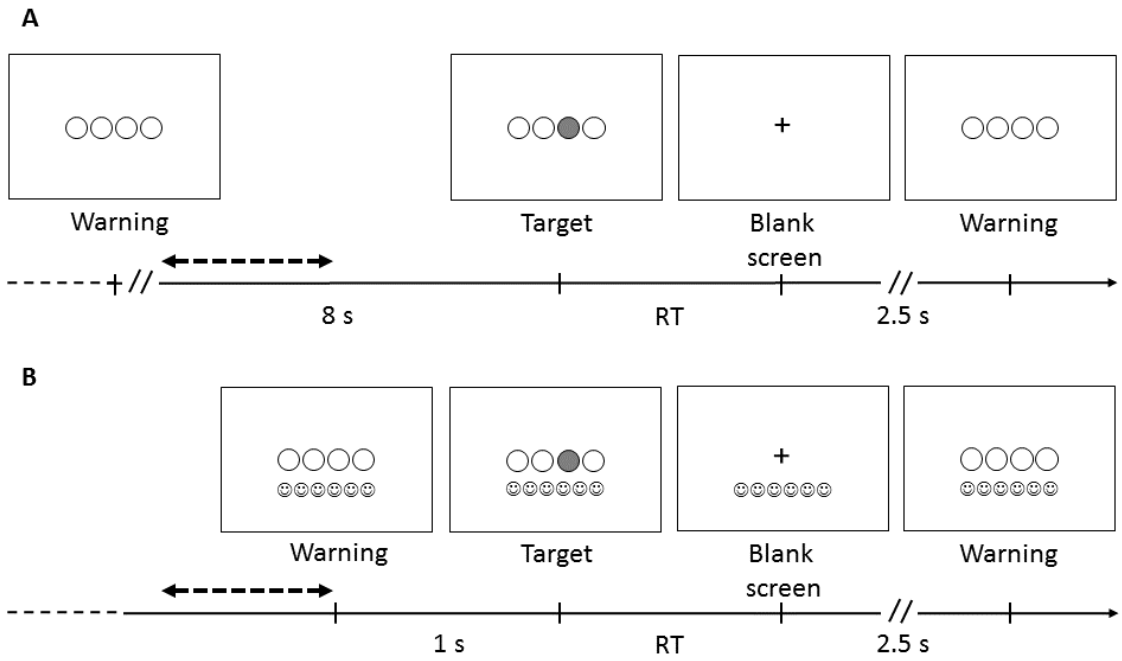

Figure S6.1. *A schematic illustration of the temporal sequence of events in the (A) baseline and (B) fast-incentive conditions of the Fast task.*
Notes: In both conditions, the target remained on the screen up to 10 s until a response (response time [RT]). The double-headed dashed window corresponds to the pre-stimulus window used to normalise the event-related spectral perturbations (ERSPs).

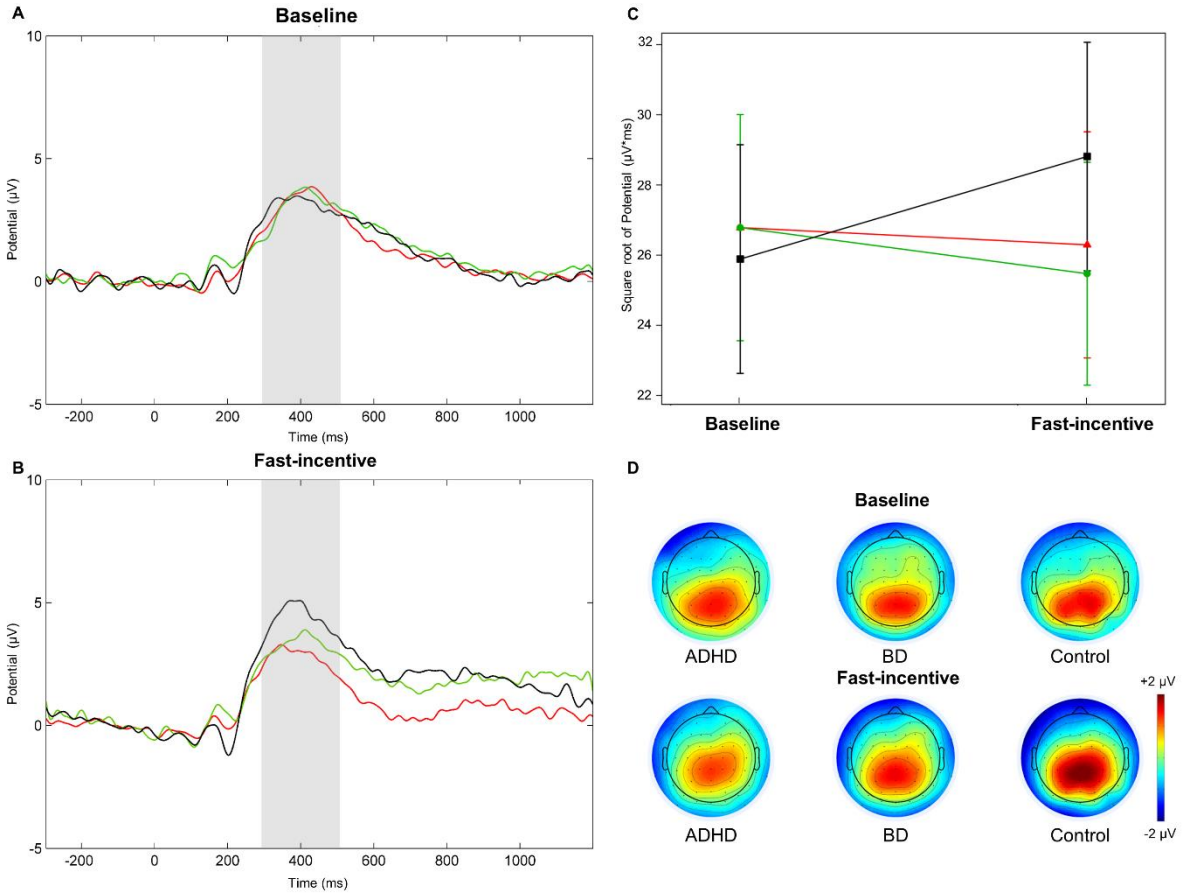

Figure S6.2. *P3 amplitude measured at Pz in the 300–500 ms window in the ADHD (in red), BD (in green) and control (in black) groups across the baseline and fast incentive conditions of the Fast task. (A) Grand average in the baseline condition; (B) Grand average in the fast-incentive condition; (C) Condition effects by group; (D) Topographic maps by group at each condition.*

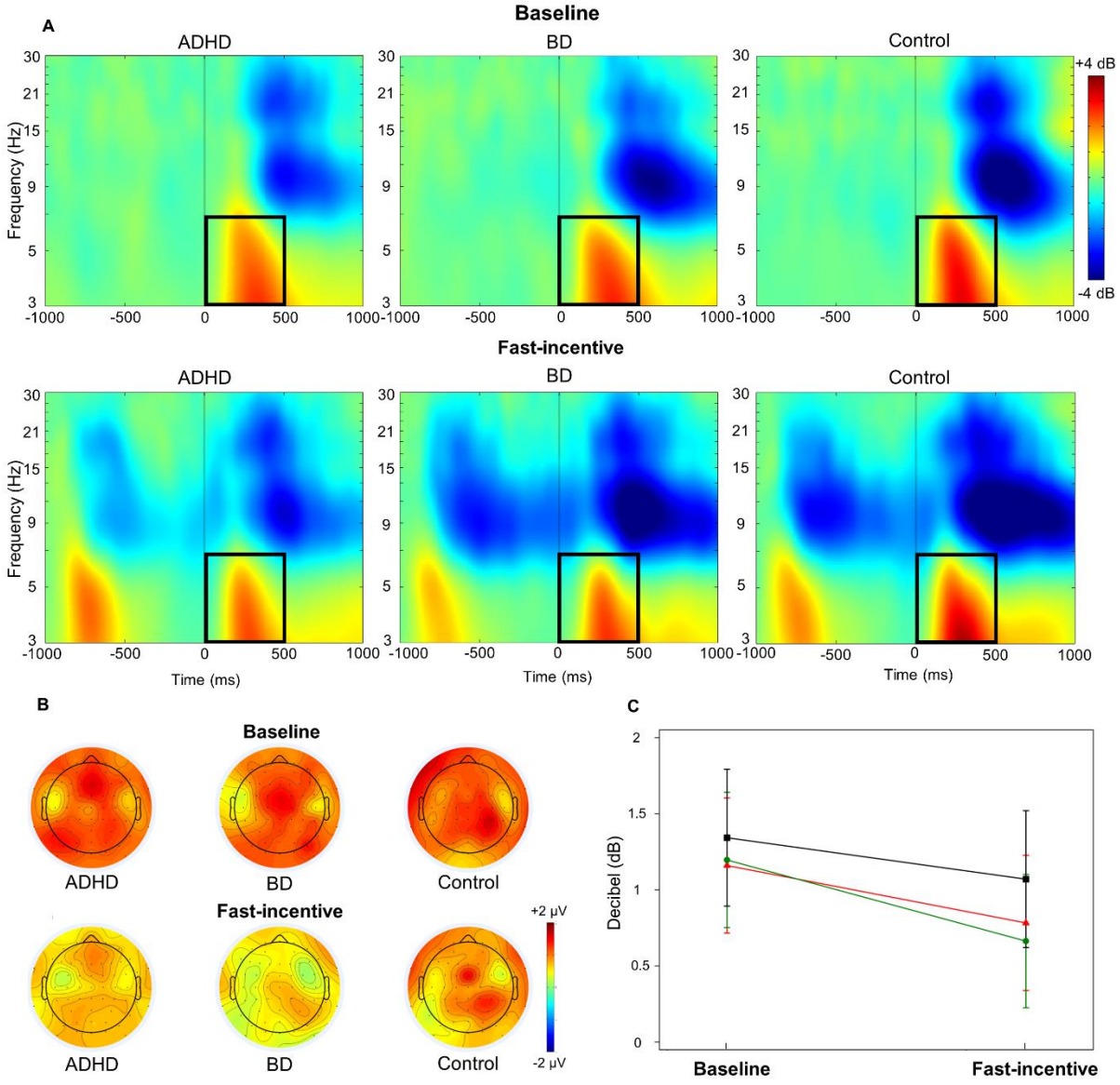

Figure S6.3. *Theta event-related spectral perturbation (ERSP) at parietal regions by group across the baseline and fast incentive conditions of the Fast task. (A) ERSP in the baseline (top) and fast-incentive (bottom) conditions; (B) Topographic maps by group in the 0-500 ms window in each condition; (C) Condition effects in the 0-500 ms window in the ADHD (in red), BD (in green) and control (in black) groups.*

12.4 Appendix E - References

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